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(54) Title: OXINDOLE DERIVATIVES

(57) Abstract: The present invention is related to oxindole derivatives, compositions containing the same, and methods of use and manufacture of the same. Such compounds generally are useful pharmacologically as agents in those disease states alleviated by the alteration of mitogen activated signaling pathways in general, and in particular in the inhibition or antagonism of protein kinases, which pathologically involve aberrant cellular proliferation. Such disease states include tumor growth, restenosis, atherosclerosis, pain and thrombosis. In particular, the present invention relates to a series of substituted oxindole compounds, which exhibit Trk family protein tyrosine kinase inhibition, and which are useful in cancer therapy and chronic pain indications.

OXINDOLE DERIVATIVES

BACKGROUND OF THE INVENTION

5 The present invention is related to oxindole derivatives, compositions containing the same, and methods of use and manufacture of the same. Such compounds generally are useful pharmacologically as agents in those disease states alleviated by the alteration of mitogen activated signaling pathways in general, and in particular in the inhibition or antagonism of protein kinases, which pathologically
10 involve aberrant cellular proliferation. Such disease states include tumor growth, restenosis, atherosclerosis, pain and thrombosis. In particular, the present invention relates to a series of substituted oxindole compounds, which exhibit Trk family protein tyrosine kinase inhibition, and which are useful in cancer therapy and chronic pain indications.

15

Cell growth, differentiation, metabolism and function are tightly controlled in higher eukaryotes. The ability of a cell to rapidly and appropriately respond to the array of external and internal signals it continually receives is of critical importance in maintaining a balance between these processes (Rozengurt, Current Opinion in
20 Cell Biology 1992, 4, 161-5; Wilks, Progress in Growth Factor Research 1990, 2, 97-111). The loss of control over cellular regulation can often lead to aberrant cell function or death, often resulting in a disease state in the parent organism.

The protein kinases represent a large family of proteins which play a central
25 role in the regulation of a wide variety of cellular processes and maintaining control over cellular function (Hanks, et al., Science 1988, 241, 42-52). A partial list of such kinases includes ab1, ATK, bcr-ab1, Blk, Brk, Btk, c-kit, c-met, c-src, CDK1, CDK2, CDK4, CDK6, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak,
30 KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie1, tie2, TRK, Yes, and Zap70.

One of the most commonly studied pathways involving kinase regulation is cellular signaling from receptors at the cell surface to the nucleus (Crews and Erikson, Cell 1993, 74, 215-7) . One example of this pathway includes a cascade of kinases in which members of the growth factor receptor tyrosine kinases (such as
5 EGF-R, PDGF-R, VEGF-R, IGF1-R, the Insulin receptor), deliver signals through phosphorylation to other kinases such as Src tyrosine kinase, and the Raf, Mek and Erk serine/threonine kinase families (Crews and Erikson, Cell 1993, 74, 215-7; Ihle, et al., Trends in Biochemical Sciences 1994, 19, 222-7). Each of these kinases is represented by several family members (Pelech and Sanghera, Trends in Biochemical
10 Sciences 1992, 17, 233-8) which play related, but functionally distinct roles. The loss of regulation of the growth factor signaling pathway is a frequent occurrence in cancer as well as other disease states.

A variety of evidence suggests that nerve growth factor (NGF) may be a
15 mediator of some persistent pain states, including neuropathic and inflammatory pain. For example: a) NGF is rapidly elevated in inflamed tissues; b) NGF specific antibodies substantially diminish inflammatory hypersensitivity; c) injection of NGF into adult rats causes a profound hypersensitivity to noxious heat and mechanical stimuli; and d) low level administration of recombinant NGF induces hyperalgesia in
20 healthy humans. NGF produces hyperalgesia through several potential mechanisms. NGF results in the upregulation of peptide neurotransmitters in neurons that detect painful stimuli (nociceptors). NGF increases the excitability of spinal cord neurons to activation. Mast cells express NGF receptors and NGF triggers the release of granules containing histamine and serotonin. Histamine and serotonin are capable
25 of sensitizing nociceptors. (Wood, John (2000) Pathology of Visceral Pain: Molecular Mechanisms and Therapeutic Implications II. Genetic Approaches to Pain Therapy. *Am. J. Physiol.* 278(40), G507-G512.)

NGF binds to two different receptors, the neurotrophin receptor p75
30 (p75NTR) and TrkA. p75NTR is a member of a family of receptors that includes

tumor necrosis factor receptor (TNFR) and FAS/AP01. These receptors have in common a cysteine-rich motif in the extracellular domain, a single transmembrane domain, and a cytoplasmic domain. p75NTR signals in a fashion similar to TNFR and FAS via the activation of NFkB, JNK, and ceramide production. The functional
5 significance of p75NTR in NGF mediated biological responses is not clear. Proposed functions include a) modulation of TrkA driven responses and b) induction of cell death in cells that express p75NTR, but not TrkA.

TrkA appears to be the primary mediator of NGF driven biological responses.
10 The most compelling evidence for this comes from NGF and TrkA knockout mice. Mice defective in either the ligand or receptor component of this system have remarkably similar phenotypes. Examples of these phenotypes include severe sensory defects characterized by a complete loss of nociceptive activity and deficiencies in thermoception. Anatomically these mice exhibit extensive peripheral nervous
15 system cell loss in trigeminal, dorsal root, and sympathetic ganglia. Other evidence for the involvement of TrkA in NGF driven responses comes from the study of the PC12 cell line. PC12 cells express high levels of p75NTR and TrkA. NGF causes PC12 cells to differentiate into a neuronal phenotype characterized by the development of axonal projections. Loss of TrkA prevents PC12 cells from differentiating in response
20 to NGF. (Eggert, A. et al (2000) Molecular Dissection of TrkA Signal Transduction Pathways Mediating Differentiation in human Neuroblastoma Cells, *Oncogene*, 19(16), 2043-2051.)

There is evidence that Trk tyrosine kinases play a role in the development of a
25 variety of cancers including, for example, breast and prostate cancer. (Guarte, J.L. et al, (1999) Expression of p75LNGFR and Trk Neurotrophin Receptors in Normal and Neoplastic Human Prostate. *BJU Int.* 84(4), 495-502; Tagliabue, E. et al, Nerve Growth Factor cooperates with p185HER2 in Activating Growth of Human Breast Carcinoma Cells, (2000) *J. Biol Chem.* 275(8), 5388-5394.) Further, there is strong
30 evidence that mediation of the Trk kinase signaling will provide beneficial biological

effects. (LeSauter, L. et al (1998) Development and Uses of Small Molecule Ligands of TrkA Receptors. *Adv. Behav. Biol.* 49, 615-625; Zhu, Z. et al (1999) Nerve Growth Factor Expression Correlates with Perineural Invasion and Pain in Human Pancreatic Cancer, *Journal of Clinical Oncology*, 17(8), 2419-28; Friess, H. et al, Nerve Growth
5 Factor and its High-Affinity Receptor in Chronic Pancreatitis (1999) *Annals of Surgery* 230(5), 615-24.)

TrkA is a receptor tyrosine kinase that belongs to a subfamily of tyrosine kinases that includes TrkB, and TrkC. TrkB and TrkC are structurally similar to TrkA,
10 but respond to different ligands in the neurotrophin family. NGF signaling through TrkA has been best characterized in the PC12 system and is similar to signal transduction mechanisms of other tyrosine kinase receptors. NGF exists as a homodimer. Binding of NGF promotes dimerization, and autophosphorylation of TrkA. Phosphorylation of TrkA increases the catalytic activity of the kinase domain
15 and creates binding sites for SH2 domain containing cytoplasmic proteins. SH2 domain binding events initiate the activation of several signal transduction pathways such as PLC γ , ras, PI3 kinase/AKT, and Raf/MEK/ERK. (Frade, J.M. et al, (1998) Nerve growth factor: two receptors, multiple functions, *BioEssays* 20: 137 – 145; Kaplan, D.R. et al, (1997) Signal transduction by the neurotrophin receptors,
20 *Current Opinion in Cell Biology*. 9: 213 – 221; Barbacid, M. (1995) Neurotrophic factors and their receptors, *Current Opinion in Cell Biology*. 7:148-155; Snider, W.D. (1994) Functions of the Neurotrophins during nervous system development: What the knockouts are teaching us, *Cell*, 77:627 – 638.)

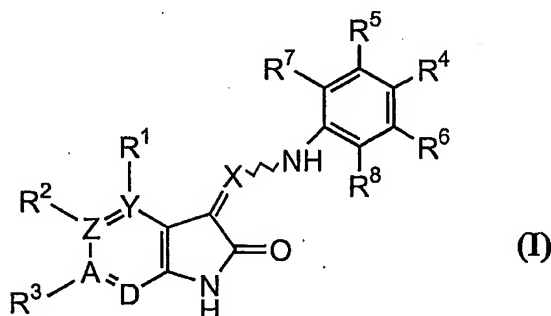
25 The selective inhibition of Trk family of kinases (TrkA, TrkB, and TrkC) is therefore an object of the present invention.

There is a continuing need in the medical field for new and more effective treatments for cancer and for the relief of pain, especially chronic pain. Because
30 TrkA and other Trk kinases may serve as a mediator of NGF driven biological

responses, inhibitors of TrkA and other Trk kinases may provide an effective treatment for cancer and for chronic pain states. At present, there is an unmet need for small molecule compounds that may be readily synthesized and are potent inhibitors of TrkA and other Trk family kinases. The present inventors have now discovered novel oxindole derivative compounds that selectively inhibit the catalytic activity of TrkA and/or other Trk family kinases thereby providing new treatment strategies for those afflicted with cancer and chronic pain. It is additionally possible that inhibitors of certain kinases may have utility in the treatment of diseases when the kinase is not misregulated, but is nonetheless essential for maintenance of the disease state.

SUMMARY OF THE INVENTION

In one aspect of the present invention, there is provided compounds of the formula (I):



15

wherein

Y, Z, A, and D are independently selected from the group consisting of: carbon and nitrogen, with the provisos that: (1) Z and D may be nitrogen, but otherwise no more than one of Y, Z, A, and D may be nitrogen, and (2) when Y, Z, or A are nitrogen, substituent R¹, R², or R³ designated for the respective nitrogen atom is non-existent;

X is selected from the group consisting of: N, CH, CCF₃, and C(C₁₋₁₂ aliphatic);

R¹ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc, Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, amino, C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic
5 aminosulfonyl, C₁₋₁₂ alkoxycarbonyl, fluoro, bromo, iodo, cyano, sulfonamide, or nitro, where R⁹, Aryl, Cyc and Het are as defined below;

R² is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, N-hydroxyimino-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, hydroxy-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxycarbonyl, carboxyl C₁₋₁₂ aliphatic, Aryl, R⁹-Aryl-oxycarbonyl, R⁹-oxycarbonyl-Aryl, Het,
10 aminocarbonyl, C₁₋₁₂ aliphatic-aminocarbonyl, Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, R⁹-Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, Het-C₁₋₁₂ aliphatic-aminocarbonyl, hydroxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂-alkoxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂ alkoxy-C₁₋₁₂ aliphatic-amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, halogen, hydroxy, C₁₋₁₂ aliphatic-sulfonyl, aminosulfonyl,
15 and C₁₋₁₂ aliphatic-aminosulfonyl, where R⁹, Aryl and Het are as defined below, with the proviso that where X is nitrogen, R² is not chloro or 3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl; or

R¹ and R² are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by a substituent
20 selected from the group consisting of: C₁₋₁₂ aliphatic, halogen, nitro, cyano, C₁₋₁₂ alkoxy, amino, hydroxyl, (R¹⁰, R¹¹)-amino, and oxo;

R³ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, hydroxy, hydroxy C₁₋₁₂ aliphatic, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxy, Aryl, Aryloxy, hydroxy-Aryl, Het, hydroxy-
25 Het, Het-oxy, or halogen, where Aryl and Het are as defined below, with the proviso that where X is nitrogen R³, is not fluoro;

R² and R³ are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₆ aliphatic or C₁₋₆ aliphatic-carbonyl;

R⁴, R⁵ and R⁶ may be the same or different and are independently selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, C₁₋₆ aliphatic-thio, di(trifluoromethyl)hydroxymethyl, carboxamide, mono-C₁₋₁₂aliphatic aminocarbonyl, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc, 5 Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, Het-oxy, amino, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic aminocarbonyl, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic alkoxy carbonyl, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic aminocarbonylamino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic alkoxy carbonylamino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonyl, Het-C₁₋₆ aliphatic aminocarbonyl, Het-C₁₋₆ aliphatic aminocarbonylamino, Het-C₁₋₆ 10 alkoxy carbonylamino, Het-C₁₋₆ aliphatic carbonyl, Het-C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl-Het-, C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic carbonylamino, (C₁₋₆ aliphatic carbonyl)(C₁₋₆ aliphatic)amino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic carbonylamino, [(R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic carbonyl][C₁₋₆ aliphatic]amino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic 15 sulfonylamino, [(R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonyl][C₁₋₆ aliphatic]amino, halogen, cyano, diethoxyphosphorylmethyl, nitro, trifluoromethyl, and trifluoromethoxy, where R⁹, R¹⁰, R¹¹, Aryl, Cyc and Het are as defined below, with the proviso that where X is nitrogen, R⁴, R⁵ and R⁶ is not nitro;

R⁷ and R⁸ may be the same or different and are independently selected from the 20 group consisting of: hydrogen, halogen, C₁₋₂ alkoxy, hydroxy, C₁₋₃-aliphatic, and C₁₋₃ aliphatic;

with the proviso that R⁴, R⁵, R⁶, R⁷, and R⁸ cannot simultaneously be hydrogen;

wherein R⁷ may additionally be optionally fused to R⁵ so as to form a fused benzo ring from the R⁵ to the R⁷ positions and

25 wherein R⁴ may additionally be optionally fused to R⁵ so as to form a fused cyclic urea ring from the R⁴ to the R⁵ positions;

R⁹ is selected from the group consisting of: C₁₋₁₂ aliphatic, hydroxy, C₁₋₁₂ alkoxy and halogen;

R¹⁰ and R¹¹ may be the same or different and are independently selected from the 30 group consisting of: hydrogen, C₁₋₆ aliphatic and Het;

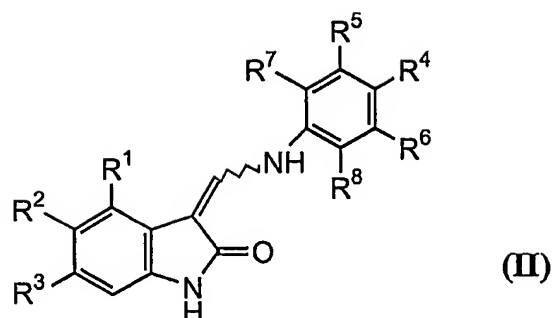
Aryl is selected from the group consisting of: phenyl, naphthyl, phenanthryl and anthracenyl;

Cyc is selected from the group consisting of: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, and optionally has one or more degrees of
5 unsaturation;

Het is a saturated or unsaturated heteroatom ring system selected from the group consisting of: benzimidazole, dihydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, isoquinoline, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine,
10 pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thiophene, thiopyran, triazine and triazole, where any of said heterocyclic rings may be optionally substituted by a substituent selected from the group consisting of: C₁₋₁₂ aliphatic, hydroxy, C₁₋₁₂ alkoxy, (R¹⁰,R¹¹)-amino, (R¹⁰,R¹¹)-
15 amino-C₁₋₁₂ aliphatic, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic amino, oxo and dioxo;

and the pharmaceutically acceptable salts, solvates, polymorphs, physiologically functional derivatives, including esters, amides, carbamates, solvates, hydrates, affinity reagents and prodrugs thereof in either crystalline or amorphous form. The esters, amides and carbamates, are preferably hydrolyzable and more preferably are
20 biohydrolyzable.

In another aspect of the present invention, there is provided compounds of formula (II),



wherein

- R¹ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc, Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, amino, C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxycarbonyl, fluoro, bromo, iodo, cyano, sulfonamide, or nitro, where R⁹, Aryl, Cyc and Het are as defined below;
- R² is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, N-hydroxyimino-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, hydroxy-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxycarbonyl, carboxyl C₁₋₁₂ aliphatic, Aryl, R⁹-Aryl-oxycarbonyl, R⁹-oxycarbonyl-Aryl, Het, aminocarbonyl, C₁₋₁₂ aliphatic-aminocarbonyl, Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, R⁹-Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, Het-C₁₋₁₂ aliphatic-aminocarbonyl, hydroxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂-alkoxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂ alkoxy-C₁₋₁₂ aliphatic-amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, halogen, hydroxy, C₁₋₁₂ aliphatic-sulfonyl, aminosulfonyl, or one or more substituents selected from the group consisting of: C₁₋₁₂ aliphatic-aminosulfonyl, where R⁹, Aryl and Het are as defined below;
- R¹ and R² are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₁₂ aliphatic, halogen, nitro, cyano, C₁₋₁₂ alkoxy, amino, hydroxyl, (R¹⁰, R¹¹)-amino, or oxo;

R³ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, hydroxy, hydroxy C₁₋₁₂ aliphatic, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxy, Aryl, Aryloxy, hydroxy-Aryl, Het, hydroxy-Het, Het-oxy, or halogen, where Aryl and Het are as defined below;

5 R² and R³ are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₆ aliphatic or C₁₋₆ aliphatic-carbonyl;

R⁴, R⁵ and R⁶ may be the same or different and are independently selected from the
 10 group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, C₁₋₆ aliphatic-thio, di(trifluoromethyl)hydroxymethyl, carboxamide, mono-C₁₋₁₂ aliphatic aminocarbonyl, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc, Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, Het-oxy, amino, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic aminocarbonyl, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic
 15 alkoxy carbonyl, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic aminocarbonylamino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic alkoxy carbonylamino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonyl, Het-C₁₋₆ aliphatic aminocarbonyl, Het-C₁₋₆ aliphatic aminocarbonylamino, Het-C₁₋₆ alkoxy carbonylamino, Het-C₁₋₆ aliphatic carbonyl, Het-C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic
 20 aminoalkyl-Het-, C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic carbonylamino, (C₁₋₆ aliphatic carbonyl)(C₁₋₆ aliphatic)amino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic carbonylamino, [(R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic carbonyl][C₁₋₆ aliphatic]amino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonylamino, [(R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonyl][C₁₋₆ aliphatic]amino, halogen, cyano, diethoxyphosphorylmethyl, nitro, trifluoromethyl, or trifluoromethoxy, where
 25 R⁹, R¹⁰, R¹¹, Aryl, Cyc and Het are as defined below;

R⁷ and R⁸ may be the same or different and are independently selected from the group consisting of: hydrogen, halogen, C₁₋₂ alkoxy, hydroxy, C₁₋₃-aliphatic and C₁₋₃ aliphatic;

with the proviso that R⁴, R⁵, R⁶, R⁷ and R⁸ cannot simultaneously be hydrogen;

wherein R⁷ may additionally be optionally fused to R⁵ so as to form a fused benzo ring from the R⁵ to the R⁷ positions; and

wherein R⁴ may additionally be optionally fused to R⁵ so as to form a fused cyclic urea ring from the R⁴ to the R⁵ positions;

5 R⁹ is selected from the group consisting of: C₁₋₁₂ aliphatic, hydroxy, C₁₋₁₂ alkoxy, or halogen;

R¹⁰ and R¹¹ may be the same or different and are independently selected from the group consisting of: hydrogen, C₁₋₆ aliphatic and Het;

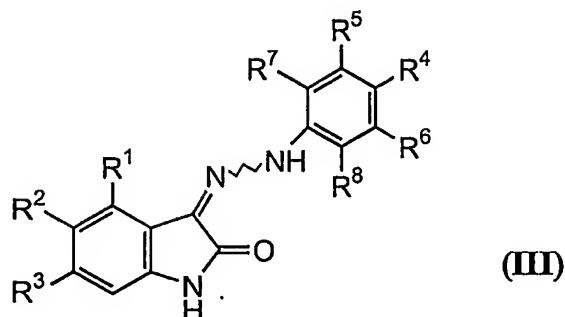
Aryl is selected from the group consisting of: phenyl, naphthyl, phenanthryl or
10 anthracenyl;

Cyc is selected from the group consisting of: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, and optionally has one or more degrees of unsaturation;

Het is a saturated or unsaturated heteroatom ring system selected from the group
15 consisting of: benzimidazole, dihydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, isoquinoline, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole,
20 thiomorpholine, thiophene, thiopyran, triazine and triazole, where any of said heterocyclic rings may be optionally substituted by a substituent selected from the group consisting of: C₁₋₁₂ aliphatic, hydroxy, C₁₋₁₂ alkoxy, (R¹⁰,R¹¹)-amino, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic amino, oxo or dioxo;

and the pharmaceutically acceptable salts, solvates, or physiologically functional
25 derivatives, including esters, amides, carbamates, solvates, hydrates, affinity reagents and prodrugs thereof in either crystalline or amorphous form. The esters, amides and carbamates, are preferably hydrolyzable and more preferably are biohydrolyzable.

In another aspect of the present invention, there is provided compounds of formula (III):



5

wherein

- R¹ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc, Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, amino, C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxycarbonyl, fluoro, bromo, iodo, cyano, sulfonamide, or nitro, where R⁹, Aryl, Cyc and Het are as defined below;
- R² is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, N-hydroxyimino-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, hydroxy-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxycarbonyl, carboxyl C₁₋₁₂ aliphatic, Aryl, R⁹-Aryl-oxycarbonyl, R⁹-oxycarbonyl-Aryl, Het, aminocarbonyl, C₁₋₁₂ aliphatic-aminocarbonyl, Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, R⁹-Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, Het-C₁₋₁₂ aliphatic-aminocarbonyl, hydroxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂-alkoxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂ alkoxy-C₁₋₁₂ aliphatic-amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, halogen, hydroxy, C₁₋₁₂ aliphatic-sulfonyl, aminosulfonyl, or one or more substituents selected from the group consisting of: C₁₋₁₂ aliphatic-

20

aminosulfonyl, where R^9 , Aryl and Het are as defined below, with the proviso that R^2 is not chloro or 3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl;

R^1 and R^2 are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₁₂ aliphatic,
 5 halogen, nitro, cyano, C₁₋₁₂ alkoxy, amino, hydroxyl, (R^{10} , R^{11})-amino, or oxo;

R^3 is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, hydroxy, hydroxy C₁₋₁₂ aliphatic, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxy, Aryl, Aryloxy, hydroxy-Aryl, Het, hydroxy-Het, Het-oxy, or halogen, where Aryl and Het are as defined below, with the proviso
 10 R^3 is not fluoro;

R^2 and R^3 are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₆ aliphatic or C₁₋₆ aliphatic-carbonyl;

15 R^4 , R^5 and R^6 may be the same or different and are independently selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, C₁₋₆ aliphatic-thio, di(trifluoromethyl)hydroxymethyl, carboxamide, mono-C₁₋₁₂aliphatic aminocarbonyl, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R^9 -Aryl-C₁₋₁₂ aliphatic, Cyc, Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, Het-oxy, amino,
 20 (R^{10} , R^{11})-amino-C₁₋₁₂ aliphatic aminocarbonyl, (R^{10} , R^{11})-amino-C₁₋₁₂ aliphatic alkoxy carbonyl, (R^{10} , R^{11})-amino-C₁₋₁₂ aliphatic aminocarbonylamino, (R^{10} , R^{11})-amino-C₁₋₆ aliphatic alkoxy carbonylamino, (R^{10} , R^{11})-amino-C₁₋₆ aliphatic sulfonyl, Het-C₁₋₆ aliphatic aminocarbonyl, Het-C₁₋₆ aliphatic aminocarbonylamino, Het-C₁₋₆ alkoxy carbonylamino, Het-C₁₋₆ aliphatic carbonyl, Het-C₁₋₆ alkoxy carbonyl, C₁₋₆
 25 aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl-Het-, C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic carbonylamino, (C₁₋₆ aliphatic carbonyl)(C₁₋₆ aliphatic)amino, (R^{10} , R^{11})-amino-C₁₋₆ aliphatic carbonylamino, [(R^{10} , R^{11})-amino-C₁₋₆ aliphatic carbonyl][C₁₋₆ aliphatic]amino, (R^{10} , R^{11})-amino-C₁₋₆ aliphatic sulfonylamino, [(R^{10} , R^{11})-amino-C₁₋₆ aliphatic sulfonyl][C₁₋₆ aliphatic]amino, halogen,
 30 cyano, diethoxyphosphorylmethyl, nitro, trifluoromethyl, or trifluoromethoxy, where

R⁹, R¹⁰, R¹¹, Aryl, Cyc and Het are as defined below, with the proviso that R⁴, R⁵ and R⁶ is not nitro;

R⁷ and R⁸ may be the same or different and are independently selected from the group consisting of: hydrogen, halogen, C₁₋₂ alkoxy, hydroxy, C₁₋₃-aliphatic and C₁₋₃ aliphatic;

with the proviso that R⁴, R⁵, R⁶, R⁷ and R⁸ cannot simultaneously be hydrogen;

R⁹ is selected from the group consisting of: C₁₋₁₂ aliphatic, hydroxy, C₁₋₁₂ alkoxy, or halogen;

R¹⁰ and R¹¹ may be the same or different and are independently selected from the group consisting of: hydrogen, C₁₋₆ aliphatic and Het;

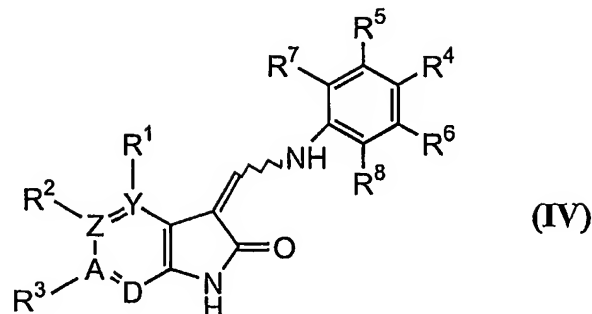
Aryl is selected from the group consisting of: phenyl, naphthyl, phenanthryl or anthracenyl;

Cyc is selected from the group consisting of: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, any one of which may have one or more degrees of unsaturation;

Het is a saturated or unsaturated heteroatom ring system selected from the group consisting of: benzimidazole, dihydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, isoquinoline, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thiophene, thiopyran, triazine and triazole, where any of said heterocyclic rings may be optionally substituted by a substituent selected from the group consisting of: C₁₋₁₂ aliphatic, hydroxy, C₁₋₁₂ alkoxy, (R¹⁰,R¹¹)-amino, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic amino, oxo or dioxo;

and the pharmaceutically acceptable salts, solvates, physiologically functional derivatives, including esters, amides, carbamates, solvates, hydrates, affinity reagents and prodrugs thereof in either crystalline or amorphous form. The esters, amides and carbamates, are preferably hydrolyzable and more preferably are biohydrolyzable.

In another aspect of the present invention, there is provided compounds of formula (IV):



5

wherein

Y, Z, A, and D are independently selected from the group consisting of: carbon and nitrogen, with the provisos that: (1) Z and D may be nitrogen, but otherwise no more than one of Y, Z, A, and D may be nitrogen, and (2) when Y, Z, or A are
 10 nitrogen, substituent R₁, R₂, or R₃ designated for the respective nitrogen atom is non-existent;

R₁ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc, Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, amino, C₁₋₁₂ aliphatic amino,
 15 di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxycarbonyl, fluoro, bromo, iodo, cyano, sulfonamide, or nitro, where R⁹, Aryl, Cyc and Het are as defined below;

R₂ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, N-hydroxyimino-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, hydroxy-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxycarbonyl,
 20 carboxyl C₁₋₁₂ aliphatic, Aryl, R⁹-Aryl-oxycarbonyl, R⁹-oxycarbonyl-Aryl, Het, aminocarbonyl, C₁₋₁₂ aliphatic-aminocarbonyl, Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, R⁹-Aryl-C₁₋₁₂ aliphatic-aminocarbonyl, Het-C₁₋₁₂ aliphatic-aminocarbonyl, hydroxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂-alkoxy-C₁₋₁₂ aliphatic-aminocarbonyl, C₁₋₁₂ alkoxy-C₁₋₁₂

aliphatic-amino, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-C₁₋₁₂ aliphatic aminosulfonyl, halogen, hydroxy, C₁₋₁₂ aliphatic-sulfonyl, aminosulfonyl, or one or more substituents selected from the group consisting of: C₁₋₁₂ aliphatic-aminosulfonyl, where R⁹, Aryl and Het are as defined below;

5 R¹ and R² are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₁₂ aliphatic, halogen, nitro, cyano, C₁₋₁₂ alkoxy, amino, hydroxyl, (R¹⁰, R¹¹)-amino, or oxo;

R³ is selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, hydroxy, hydroxy C₁₋₁₂ aliphatic, di-C₁₋₁₂ aliphatic amino, di-C₁₋₁₂ aliphatic aminocarbonyl, di-
10 C₁₋₁₂ aliphatic aminosulfonyl, C₁₋₁₂ alkoxy, Aryl, Aryloxy, hydroxy-Aryl, Het, hydroxy-Het, Het-oxy, or halogen, where Aryl and Het are as defined below;

R² and R³ are optionally joined to form a fused ring selected from the group as defined for Het below, and said fused ring is optionally substituted by C₁₋₆ aliphatic or C₁₋₆ aliphatic-carbonyl;

15

R⁴, R⁵ and R⁶ may be the same or different and are independently selected from the group consisting of: hydrogen, C₁₋₁₂ aliphatic, thiol, C₁₋₆ aliphatic-thio, di(trifluoromethyl)hydroxymethyl, carboxamide, mono-C₁₋₁₂aliphatic aminocarbonyl, hydroxy, hydroxy-C₁₋₁₂ aliphatic, Aryl, Aryl-C₁₋₁₂ aliphatic, R⁹-Aryl-C₁₋₁₂ aliphatic, Cyc,
20 Cyc-C₁₋₆ aliphatic, Het, Het-C₁₋₁₂ aliphatic, C₁₋₁₂ alkoxy, Aryloxy, Het-oxy, amino, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic aminocarbonyl, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic alkoxy carbonyl, (R¹⁰,R¹¹)-amino-C₁₋₁₂ aliphatic aminocarbonylamino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic alkoxy carbonylamino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonyl, Het-C₁₋₆ aliphatic aminocarbonyl, Het-C₁₋₆ aliphatic aminocarbonylamino, Het-C₁₋₆
25 alkoxy carbonylamino, Het-C₁₋₆ aliphatic carbonyl, Het-C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl, C₁₋₆ aliphatic sulfonyl-C₁₋₆ aliphatic aminoalkyl-Het-, C₁₋₆ alkoxy carbonyl, C₁₋₆ aliphatic carbonylamino, (C₁₋₆ aliphatic carbonyl)(C₁₋₆ aliphatic)amino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic carbonylamino, [(R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic carbonyl][C₁₋₆ aliphatic]amino, (R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic
30 sulfonylamino, [(R¹⁰,R¹¹)-amino-C₁₋₆ aliphatic sulfonyl][C₁₋₆ aliphatic]amino, halogen,

cyano, diethoxyphosphorylmethyl, nitro, trifluoromethyl, or trifluoromethoxy, where R^9 , R^{10} , R^{11} , Aryl, Cyc and Het are as defined below;

R^7 and R^8 may be the same or different and are independently selected from the group consisting of: hydrogen, halogen, C_{1-2} alkoxy, hydroxy, C_{1-3} -aliphatic and C_{1-3} aliphatic;

with the proviso that R^4 , R^5 , R^6 , R^7 and R^8 cannot simultaneously be hydrogen;

wherein R^7 may additionally be optionally fused to R^5 so as to form a fused benzo ring from the R^5 to the R^7 positions; and

wherein R^4 may additionally be optionally fused to R^5 so as to form a fused cyclic urea ring from the R^4 to the R^5 positions;

R^9 is selected from the group consisting of: C_{1-12} aliphatic, hydroxy, C_{1-12} alkoxy, or halogen;

R^{10} and R^{11} may be the same or different and are independently selected from the group consisting of: hydrogen, C_{1-6} aliphatic and Het;

Aryl is selected from the group consisting of: phenyl, naphthyl, phenanthryl or anthracenyl;

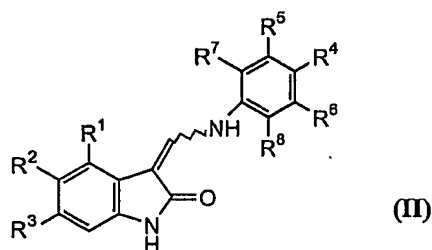
Cyc is selected from the group consisting of: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, and optionally has one or more degrees of unsaturation;

Het is a saturated or unsaturated heteroatom ring system selected from the group consisting of: benzimidazole, dihydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, isoquinoline, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiatriazole, thiazine, thiazole, thiomorpholine, thiophene, thiopyran, triazine and triazole, where any of said heterocyclic rings may be optionally substituted by a substituent selected from the group consisting of: C_{1-12} aliphatic, hydroxy, C_{1-12} alkoxy, (R^{10}, R^{11}) -amino, (R^{10}, R^{11}) -amino- C_{1-12} aliphatic, (R^{10}, R^{11}) -amino- C_{1-12} aliphatic amino, oxo or dioxo;

and the pharmaceutically acceptable salts, solvates, physiologically functional derivatives, including esters, amides, carbamates, solvates, hydrates, affinity reagents and prodrugs thereof in either crystalline or amorphous form. The esters, amides and carbamates, are preferably hydrolyzable and more preferably are biohydrolyzable.

5.

In another aspect of the present invention is a compound of the formula II:



10

or salts, solvates, or physiological functional derivatives thereof

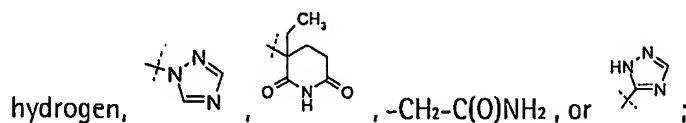
wherein:

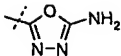
15 R^1 is hydrogen;

R^2 is hydrogen; or

R^1 and R^2 are optionally joined to form a fused ring Het, wherein Het is a triazole ring;

R^3 is hydrogen;

20 R^4 is selected from the group consisting of

R⁵ is hydrogen or , or

R⁴ and R⁵ are optionally joined to form a fused cyclic urea ring; and

5

R⁶, R⁷, and R⁸ are hydrogen.

While the ensuing discussion refers to the compound of formula (I), it will be
10 understood that the compounds of formula (I) includes the compounds of formulas
(II), (III) and (IV); accordingly, references hereafter to formula (I) should hereafter be
understood to includes the compounds of formulas (II), (III) and (IV) as well as the
compounds of formula (I).

15 Due to the presence of an oxindole exocyclic double bond, also included in
the compounds of the invention are their respective pure E and Z geometric isomers
as well as mixtures of E and Z isomers. The invention as described and claimed does
not set any limiting ratios on prevalence of Z to E isomers.

20 Likewise, it is understood that compounds of formula (I) as used herein
includes all tautomeric forms other than the specific tautomer represented by the
formula.

Certain of the compounds as described contain one or more chiral, or
25 asymmetric, centers and are therefore be capable of existing as optical isomers that
are either dextrorotatory or levorotatory. Also included in the compounds of the
invention are the respective dextrorotatory or levorotatory pure preparations, and
mixtures thereof.

Certain compounds of formula (I) above are optionally provided in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereoisomers) and mixtures of these are included within the scope of the present invention. Likewise, it is understood that compounds of formula (I) are optionally provided in various tautomeric forms within the scope of the present invention.

The present invention also provides compounds of formula (I) and pharmaceutically acceptable salts thereof (hereafter collectively referred to as the "active compounds") for use in therapy, and particularly in the treatment of disorders mediated by a kinase, such as TrkA tyrosine kinase, including, for example, cancers and chronic pain. In a further embodiment, the disorder involves abnormal angiogenesis, such as arthritis, diabetic retinopathy, macular degeneration and psoriasis.

15

A further aspect of the invention provides a method of treating a disorder in a mammal, said disorder mediated by inappropriate mitogen activated kinase activity, including administering to said mammal a therapeutically effective amount of a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof. In one embodiment, the disorder is cancer. In another embodiment the disorder is chronic pain. In a further embodiment, the disorder involves abnormal angiogenesis, such as arthritis, diabetic retinopathy, macular degeneration and psoriasis.

In a related aspect the present invention comprises a method for inhibiting a kinase comprising bringing said kinase into contact with a compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof.

Another aspect of the present invention provides for the use of a compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof, in

the preparation of a medicament for the treatment of a disorder mediated by inappropriate TrkA activity. In one embodiment, the disorder is cancer. In another embodiment, the disorder is chronic pain. In a further embodiment, the disorder involves abnormal angiogenesis, such as arthritis, diabetic retinopathy, macular
5 degeneration and psoriasis.

Additionally, compounds of formula (I) or salts, solvates, or physiologically functional derivatives thereof, can be used in the preparation of a medicament for the treatment of organ transplant rejection, tumor growth, chemotherapy-induced
10 mucositis, radiation-induced mucositis, plantar-palmar syndrome, chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia and hirsutism or of treating a disease state selected from the group consisting of: mucocitis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, glomerulonephritis, diabetic nephropathy, malignant
15 nephrosclerosis, chronic obstructive pulmonary disease, thrombotic microangiopathy, aglomerulopathy, psoriasis, diabetes mellitus, inflammation, a neurodegenerative disease, macular degeneration, actinic keratosis and hyperproliferative disorders.

Another aspect of the present invention provides the use of an active
20 compound of formula (I), in co-administration or alternating administration with previously known anti-tumor therapies for more effective treatment of such tumors.

Other aspects of the present invention related to the inhibition of protein kinases are discussed in more detail below.

25

The inappropriate TrkA activity referred to herein is any TrkA activity that deviates from the normal TrkA activity expected in a particular mammalian subject. Inappropriate TrkA activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of TrkA activity.
30 Such inappropriate activity may result then, for example, from overexpression or

mutation of the protein kinase leading to inappropriate or uncontrolled activation. Furthermore, it is also understood that unwanted TrkA activity may reside in an abnormal source, such as a malignancy. That is, the level of TrkA activity does not have to be abnormal to be considered inappropriate, rather the activity derives from
5 an abnormal source.

Compounds synthesized as part of the present invention, which are currently preferred, are listed in Tables 1 below. Compounds are identified by the numbers shown in the first column; variables below in the rest of the columns are with
10 reference to the generic structure (II). Corresponding IUPAC nomenclature are disclosed in Table 2. Since all substituents at each point of substitution are capable of independent synthesis of each other, the tables are to be read as a matrix in which any combination of substituents is within the scope of the disclosure and claims of the invention.

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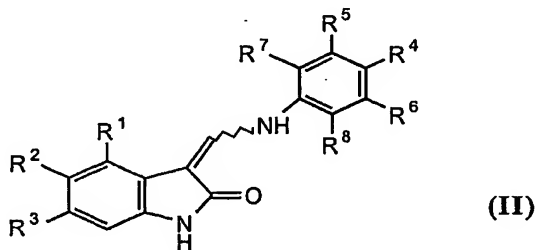

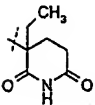
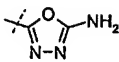



Table 1

Example	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>R⁴</u>	<u>R⁵</u>	<u>R⁶</u>	<u>R⁷</u>	<u>R⁸</u>
1	H	H	H		-NHC(O)NH-	H	H	H
2	H	H	H		H	H	H	H
3	H	H	H		H	H	H	H
4		-NH-N=N-	H	H		H	H	H
5	H	H	H	-CH ₂ -C(O)NH ₂	H	H	H	H
6	H	H	H		H	H	H	H

5

Standard accepted nomenclature corresponding to the Examples set forth in this specification are set forth below. In some cases nomenclature is given for one or more possible isomers.

TABLE 2

Example 1	5-{[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}-1,3-dihydro-2H-benzimidazol-2-one
Example 2	(3Z)-3-{[4-(1H-1,2,4-triazol-1-yl)anilino]methylene}-1,3-dihydro-2H-indol-2-one
Example 3	3-ethyl-3-(4-{[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}phenyl)-2,6-piperidinedione
Example 4	(8Z)-8-{[3-(5-amino-1,3,4-oxadiazol-2-yl)anilino]methylene}-6,8-dihydro[1,2,3]triazolo[4,5-e]indol-7(3H)-one
Example 5	2-(4-{[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}phenyl)acetamide
Example 6	(3Z)-3-{[4-(1H-1,2,4-triazol-3-yl)anilino]methylene}-1,3-dihydro-2H-indol-2-one

The invention discloses thirteen different points of substitution on structural
 5 formula (I). Each of these points of substitution bears a substituent whose selection and synthesis as part of this invention is independent of all other points of substitution on formula (I). Each point of substitution is now further described.

Preferred substitutions for Y, Z, A and D are nitrogen or carbon. The most
 10 preferred substituents for D are nitrogen and carbon. The most highly preferred substituent for Y, Z, A and D is carbon.

Preferred substitutions at the R¹ position include hydrogen, fluoro, bromo, iodo, lower alkyl, cyano and nitro. Alternatively, R¹ is optionally joined with R² to
 15 form a fused ring structure selected from the group consisting of: thiazole, imidazole, triazole and pyridine. Further, such fused ring structures are optionally

substituted by one or more substituents selected from the group consisting of: halogen, amino, lower alkyl substituted amino, lower alkyl and lower alkyl carbonyl. In a preferred embodiment, R^1 is selected from the group, which includes hydrogen and methyl, or R^1 is fused with R^2 to form a ring structure selected from the group, 5 which includes fused thiazole, fused triazole, and fused pyridine. In another preferred embodiment, R^1 is fused with R^2 to form a ring structure selected from the group, which includes fused thiazole, pyridine and pyridine substituted by halogen or methyl.

10 Preferred substitutions at the R^2 position include hydrogen, lower alkyl, lower alkoxy, hydroxy lower alkyl, C_{1-12} alkoxy carbonyl, Aryl, Het, aminocarbonyl, lower alkyl aminocarbonyl, halogen and hydroxy. Alternatively, R^2 is fused with R^1 to form a fused ring selected from the group, which includes thiazole, imidazole, triazole and pyridine. Such fused rings are optionally substituted by a substituent selected from 15 the group, which includes halogen, amino, lower alkyl substituted amino, lower alkyl and lower alkyl carbonyl. Most preferably, R^2 is selected from the group, which includes hydroxyl, hydroxy and lower alkyl, or is fused with R^1 to form a ring structure selected from the group, which includes fused thiazole, fused triazole, and fused pyridine. In another preferred embodiment, R^2 is selected from the group 20 which includes hydroxy and hydroxymethyl, or is fused with R^1 to form a fused ring from the group which includes fused thiazole, pyridine and pyridine substituted by halogen or methyl.

Preferred substitutions at R^3 include hydrogen, lower alkyl, lower alkenyl, 25 halogen, phenyl, Het and alkoxy. Most preferred are hydrogen, halogen, ethenyl and methyl. Most highly preferred substitutions at R^3 are hydrogen and bromo.

Preferred substitutions at R^4 include hydrogen, lower alkyl, hydroxy, hydroxy- 30 lower alkyl, carboxamide, mono- lower alkyl aminocarbonyl, substituted Aryl-lower alkyl, Het, Het-lower alkyl, lower alkoxy, Aryloxy, Het-oxy, amino, mono- or di-

lower alkyl-amino lower alkyl aminocarbonyl, mono- or di- lower alkyl-amino lower alkoxy carbonyl, mono- or di-lower alkyl-amino lower alkyl aminocarbonylamino, mono- or di- lower alkyl-amino lower alkoxy carbonylamino, lower alkyl carbonylamino, (lower alkyl carbonyl)(lower alkyl)amino, mono- or di-lower alkyl-amino lower alkyl carbonylamino, [mono- or di-lower alkyl-amino lower alkyl carbonyl][lower alkyl]amino, mono- or di-lower alkyl-amino lower alkyl sulfonylamino, [mono- or di-lower alkyl-amino lower alkyl sulfonyl][lower alkyl]amino, mono- or di- lower alkyl-amino lower alkyl sulfonyl, Het lower alkyl aminocarbonyl, Het lower alkyl aminocarbonylamino, Het lower alkoxy carbonylamino, Het lower alkyl carbonyl, Het lower alkoxy carbonyl, lower alkyl sulfonyl lower alkyl aminoalkyl, lower alkyl sulfonyl-lower alkyl-aminoalkyl-Het-, lower alkoxy carbonyl, halogen, cyano, diethoxyphosphorylmethyl, trifluoromethyl and trifluoromethoxy. The most preferred substitutions are lower alkyl, hydroxy, hydroxy-lower alkyl, carboxamide, mono- lower alkyl aminocarbonyl, substituted Aryl-lower alkyl, Het, Het-lower alkyl, Het-oxy, mono- or di- lower alkyl-amino lower alkyl aminocarbonyl, mono- or di- lower alkyl-amino lower alkoxy carbonyl, mono- or di-lower alkyl-amino lower alkyl aminocarbonylamino, mono- or di- lower alkyl-amino lower alkoxy carbonylamino, lower alkyl carbonylamino, (lower alkyl carbonyl)(lower alkyl)amino, mono- or di-lower alkyl-amino lower alkyl carbonylamino, [mono- or di-lower alkyl-amino lower alkyl carbonyl][lower alkyl]amino, mono- or di-lower alkyl-amino lower alkyl sulfonylamino, [mono- or di-lower alkyl-amino lower alkyl sulfonyl][lower alkyl]amino, mono- or di- lower alkyl-amino lower alkyl sulfonyl, Het lower alkyl aminocarbonyl, Het lower alkyl carbonyl, lower alkyl sulfonyl lower alkyl aminoalkyl, lower alkyl sulfonyl-lower alkyl-aminoalkyl-Het-, halogen, cyano and trifluoromethyl. Most highly preferred are hydroxymethyl, hydroxyethyl, 4-pyridylmethyl, 4-morpholino, acetamido, N-methylacetamido, carboxamide, diethylaminoethylsulfonyl, 5-methyl-3-pyrazolon-1-yl and 3-ethyl-piperidine-2,6-dion-3-yl.

Preferred substitutions at R⁵ include hydrogen, lower alkyl, hydroxy, hydroxy-lower alkyl, carboxamide, mono- lower alkyl aminocarbonyl, substituted Aryl-lower alkyl, Het, Het-lower alkyl, lower alkoxy, Aryloxy, Het-oxy, amino, mono- or di-lower alkyl-amino lower alkyl aminocarbonyl, mono- or di- lower alkyl-amino lower

5 alkoxy carbonyl, mono- or di-lower alkyl-amino lower alkyl aminocarbonylamino, mono- or di- lower alkyl-amino lower alkoxy carbonylamino, lower alkyl carbonylamino, (lower alkyl carbonyl)(lower alkyl)amino, mono- or di-lower alkyl-amino lower alkyl carbonylamino, [mono- or di-lower alkyl-amino lower alkyl carbonyl][lower alkyl]amino, mono- or di-lower alkyl-amino lower alkyl

10 sulfonylamino, [mono- or di-lower alkyl-amino lower alkyl sulfonyl][lower alkyl]amino, mono- or di- lower alkyl-amino lower alkyl sulfonyl, Het lower alkyl aminocarbonyl, Het lower alkyl aminocarbonylamino, Het lower alkoxy carbonylamino, Het lower alkyl carbonyl, Het lower alkoxy carbonyl, lower alkyl sulfonyl lower alkyl aminoalkyl, lower alkyl sulfonyl-lower alkyl-aminoalkyl-Het-,

15 lower alkoxy carbonyl, halogen, cyano, diethoxyphosphorylmethyl, trifluoromethyl and trifluoromethoxy. The most preferred substitutions are lower alkyl, hydroxy, hydroxy-lower alkyl, carboxamide, mono- lower alkyl aminocarbonyl, substituted Aryl-lower alkyl, Het, Het-lower alkyl, Het-oxy, mono- or di- lower alkyl-amino lower alkyl aminocarbonyl, mono- or di- lower alkyl-amino lower alkoxy carbonyl, mono-

20 or di-lower alkyl-amino lower alkyl aminocarbonylamino, mono- or di- lower alkyl-amino lower alkoxy carbonylamino, lower alkyl carbonylamino, (lower alkyl carbonyl)(lower alkyl) amino, mono- or di-lower alkyl-amino lower alkyl carbonylamino, [mono- or di-lower alkyl-amino lower alkyl carbonyl][lower alkyl]amino, mono- or di-lower alkyl-amino lower alkyl sulfonylamino, [mono- or di-

25 lower alkyl-amino lower alkyl sulfonyl][lower alkyl]amino, mono- or di- lower alkyl-amino lower alkyl sulfonyl, Het lower alkyl aminocarbonyl, Het lower alkyl carbonyl, lower alkyl sulfonyl lower alkyl aminoalkyl, lower alkyl sulfonyl-lower alkyl-aminoalkyl-Het-, halogen, cyano and trifluoromethyl. Most highly preferred are hydroxymethyl, hydroxyethyl, 4-pyridylmethyl, 4-morpholino, acetamido, N-

methylacetamido, carboxamide, diethylaminoethylsulfonyl, 5-methyl-3-pyrazolon-1-yl and 3-ethyl-piperidine-2,6-dion-3-yl.

The most preferred substitution at R⁶ is hydrogen.

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Preferred substitutions at R⁷ and R⁸ are hydrogen, halogen and methyl.

Another preferred substitution at R⁷ includes the state in which R⁷ is joined to R⁵ so as to form a fused benzo ring from R⁵ to R⁷.

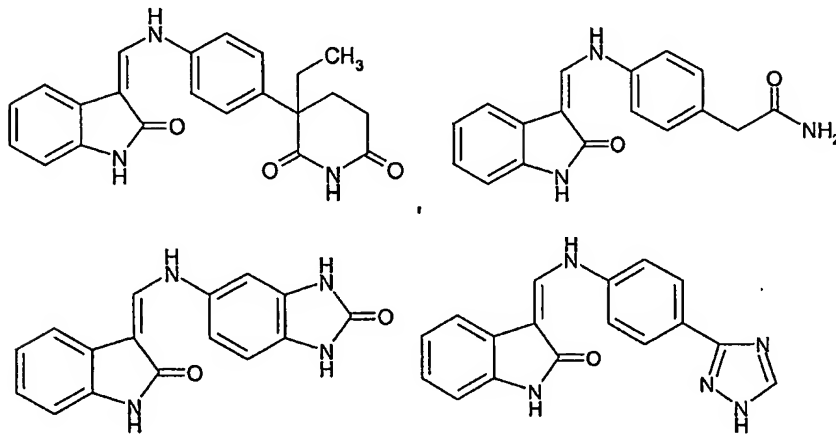
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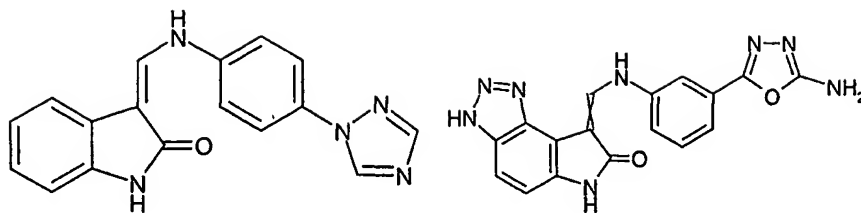
Another preferred substitution at R⁴ includes the state in which R⁴ is joined to R⁵ so as to form a fused cyclic urea ring from R⁴ to R⁵

Preferred substitutions at X include N, CH and CCH₃. Most preferred is CH.

15

Highly preferred compounds include





DETAILED DESCRIPTION OF THE INVENTION

5 Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, 10 Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Diethanolamine, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollyarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, 15 Mesylate, Metaphosphoric, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Trifluoroacetate, Triethiodide, 20 Trimethylammonium and Valerate.

Other salts, which are not pharmaceutically acceptable, may be useful in the preparation of compounds of formula (I) and these form a further aspect of the invention.

Also included within the scope of the invention are the individual isomers of the compounds represented by formula (I) above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers the individual isomers of the compounds represented by formula above as mixtures with isomers
5 thereof in which one or more chiral asymmetric centers are inverted.

As used herein, the term "aliphatic" refers to the terms alkyl, alkylene, alkenyl, alkenylene, alkynyl and alkynylene.

10 As used herein, the term "lower" refers to a group having between one and six carbons.

As used herein, the term "alkyl" refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with
15 substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by a substituent selected from the group including alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of
20 substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, n-butyl, n-pentyl, isobutyl, isopropyl and the like.

As used herein, the term "alkylene" refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally
25 substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being

allowed. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

As used herein, the term "alkenyl" refers to a hydrocarbon radical having
5 from two to ten carbons and at least one carbon-carbon double bond, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro,
10 cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed.

As used herein, the term "alkenylene" refers to an straight or branched chain divalent hydrocarbon radical having from two to ten carbon atoms and one or more
15 carbon - carbon double bonds, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen and lower
20 perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkenylene" as used herein include, but are not limited to, ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like.

As used herein, the term "alkynyl" refers to a hydrocarbon radical having
25 from two to ten carbons and at least one carbon-carbon triple bond, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro,

cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed.

As used herein, the term "alkynylene" refers to a straight or branched chain
5 divalent hydrocarbon radical having from two to ten carbon atoms and one or more
carbon - carbon triple bonds, optionally substituted with substituents selected from
the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower
alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally
substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl,
10 aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen and lower
perfluoroalkyl, multiple degrees of substitution being allowed. Examples of
"alkynylene" as used herein include, but are not limited to, ethyne-1,2-diyl, propyne-
1,3-diyl, and the like.

15 As used herein, the term "cycloaliphatic" includes the terms cycloalkyl,
cycloalkylene, cycloalkenyl, cycloalkenylene, cycloalkynyl and cycloalkylnylene.

As used herein, "cycloalkyl" refers to a alicyclic hydrocarbon group with one
or more degrees of unsaturation, having from three to twelve carbon atoms,
20 optionally substituted with substituents selected from the group which includes
lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl,
oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl
optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro,
cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being
25 allowed. "Cycloalkyl" includes by way of Example cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

As used herein, the term "cycloalkylene" refers to a non-aromatic alicyclic
divalent hydrocarbon radical having from three to twelve carbon atoms, optionally
30 substituted with substituents selected from the group which includes lower alkyl,

lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed.

5 Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl, cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "cycloalkenyl" refers to a substituted alicyclic hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 1-cyclopentene-3-yl, 1-cyclohexene-3-yl, 1-cycloheptene-4-yl, and the like.

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As used herein, the term "cycloalkenylene" refers to a substituted alicyclic divalent hydrocarbon radical having from three to twelve carbon atoms and at least one carbon-carbon double bond in the ring system, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "cycloalkenylene" as used herein include, but are not limited to, 4,5-cyclopentene-1,3-diyl, 3,4-cyclohexene-1,1-diyl, and the like.

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As used herein, the term "heteroatom ring system" refers to the terms heterocyclic, heterocyclyl, heteroaryl and heteroarylene. Non-limiting examples of such heteroatom ring systems are recited in the Summary of the Invention, above.

5 As used herein, the term "heterocyclic" or the term "heterocyclyl" refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower
10 alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic" include, but
15 are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" refers to a three to twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation
20 containing one or more heteroatoms selected from S, SO, SO₂, O, or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro,
25 cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-2,4-diyl,

piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" refers to a benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form ring systems such as anthracene, phenanthrene and naphthalene, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of aryl include, but are not limited to, phenyl, 2-naphthyl, 1-naphthyl, biphenyl, and the like.

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As used herein, the term "arylene" refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to, benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "heteroaryl" refers to a five - to seven - membered aromatic ring, or to a polycyclic heterocyclic aromatic ring, containing one or more nitrogen, oxygen, or sulfur heteroatoms at any position, where N-oxides and sulfur

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monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring systems, one or more of the rings may contain one or more heteroatoms. Examples of "heteroaryl" used herein are furan, thiophene, pyrrole, imidazole, pyrazole, triazole, tetrazole, thiazole, oxazole, isoxazole, oxadiazole, thiadiazole, isothiazole, pyridine, pyridazine, pyrazine, pyrimidine, quinoline, isoquinoline, benzofuran, benzothiophene, indole and indazole, and the like.

As used herein, the term "heteroarylene" refers to a five - to seven - membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of: lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,4-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

As used herein, the term "alkoxy" refers to the group R_aO- , where R_a is aliphatic.

5 As used herein, the term "alkylsulfanyl" refers to the group R_aS- , where R_a is aliphatic.

As used herein, the term "alkylsulfenyl" refers to the group $R_aS(O)-$, where R_a is aliphatic.

10

As used herein, the term "alkylsulfonyl" refers to the group R_aSO_2- , where R_a is aliphatic.

As used herein, the term "acyl" refers to the group $R_aC(O)-$, where R_a is
15 aliphatic, cycloaliphatic, or heterocyclyl.

As used herein, the term "aroyl" refers to the group $R_aC(O)-$, where R_a is aryl.

As used herein, the term "heteroaroyl" refers to the group $R_aC(O)-$, where R_a is heteroaryl.

20

As used herein, the term "alkoxycarbonyl" refers to the group $R_aOC(O)-$, where R_a is aliphatic.

As used herein, the term "acyloxy" refers to the group $R_aC(O)O-$, where R_a is
25 aliphatic, cycloaliphatic, or heterocyclyl.

As used herein, the term "aroyloxy" refers to the group $R_aC(O)O-$, where R_a is aryl.

As used herein, the term "heteroaroxyloxy" refers to the group $R_aC(O)O-$, where R_a is heteroaryl.

As used herein, the term "optionally" is inclusive of circumstances in which
5 described condition is present and circumstances in which the described condition is not present, for example, where the term is used with reference to a chemical substituent, it indicates the inclusion of embodiments in which the specified substituent is present as well as embodiments in which the specified substituent is not present.

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As used herein, the term "substituted" indicates the presence of the named substituent or substituents, and includes multiple degrees of substitution.

As used herein, the terms "contain" or "containing" with reference to alkyl,
15 alkenyl, alkynyl or cycloalkyl substituents indicates in-line substitution(s) with one or more substituents at any position along the alkyl, alkenyl, alkynyl or cycloalkyl substituents, such as one or more of any of O, S, SO, SO₂, N, or N-alkyl, including, for example, $-CH_2-O-CH_2-$, $-CH_2-SO_2-CH_2-$, $-CH_2-NH-CH_3$ and so forth.

20 As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol, or acetic acid.

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The compounds of the present invention have the ability to crystallize in more than one form, a characteristic that is known as polymorphism, and such polymorphic forms ("polymorphs") are within the scope of the present invention. Polymorphism generally can occur as a response to changes in temperature or
30 pressure or both and can also result from variations in the crystallization process.

Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility, and melting point.

As used herein, the term "physiologically functional derivative" refers to any
5 pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal
10 Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives. Including within the scope of the term are the terms "biohydrolyzable carbonate", "biohydrolyzable ureide", "biohydrolyzable carbamate", "biohydrolyzable ester", and "biohydrolyzable amide".

15

As used herein, the terms "biohydrolyzable carbonate", "biohydrolyzable ureide" and "biohydrolyzable carbamate" include carbonates, ureides, and carbamates, respectively, of a compound of the general formula (I) which carbonates, ureides, and carbamates, do not completely diminish the biological
20 activity of the parent substance. Such carbonates, ureides, and carbamates may confer on the parent compound of the general formula (I) advantageous properties *in vivo*, such as improved duration of action, onset of action, and the like. Also included are compounds which are relatively biologically inactive but which are converted *in vivo* by the subject to the biologically active principle. An advantage of
25 such biohydrolyzable forms is that, for example, they facilitate improved oral administration because the carbonates, ureides, and carbamates are more readily absorbed from the gut and are then transformed to a compound of formula (I) in plasma. Many examples of such biohydrolyzable compounds are known in the art and include, by way of example, lower alkyl carbamates.

30

As used herein, the term "biohydrolyzable ester" is an ester of a compound of general formula, which does not completely diminish the biological activity of the parent substance. Such esters may confer on the parent compound of the general formula (I) advantageous properties *in vivo*, such as improved duration of action, onset of action, and the like. Also included are esters which are relatively biologically inactive but which are converted *in vivo* by the subject to the biologically active principle. An advantage of such biohydrolyzable forms is that, for example, they facilitate improved oral administration because they are more readily absorbed from the gut and are then transformed to a compound of formula (I) in plasma. Many examples of such biohydrolyzable esters are known in the art and include, by way of example, lower alkyl esters, lower acyloxy-alkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters and choline esters.

As used herein, the term "biohydrolyzable amide" is an amide of a compound of general formula, which does not completely diminish the biological activity of the parent substance. Such amides may confer on the parent compound of the general formula (I) advantageous properties *in vivo*, such as improved duration of action, onset of action, and the like. Also included are amides which are relatively biologically inactive but which are converted *in vivo* by the subject to the biologically active principle. An advantage of such biohydrolyzable forms is that, for example, they facilitate improved oral administration because they are more readily absorbed from the gut and are then transformed to a compound of formula (I) in plasma. Many examples of such biohydrolyzable are known in the art and include, by way of example, lower alkyl amides, α -amino acid amides, alkoxyacyl amides and alkylaminoalkylcarbonyl amides.

As used herein, the term "prodrug" includes compounds, which are hydrolyzable *in vivo* to yield an active compound of formula (I), including for example, biohydrolyzable amides, biohydrolyzable esters and biohydrolyzable

carbamates. The term "prodrug" also includes compounds in which the biohydrolyzable functionality is encompassed in the compound of formula (I): for example, a lactam formed by a carboxylic group in R₁ and an amine in R₂, and compounds which may be oxidized or reduced biologically at a given functional
5 group to yield drug substances of formula (I). Examples of such functional groups are, but are not limited to, 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

As used herein, the term "affinity reagent" means a group attached to the
10 compound of formula (I) which does not affect its in vitro biological activity, allowing the compound to bind to a target, yet such a group binds strongly to a third component allowing a) characterization of the target as to localization within a cell or other organism component, perhaps by visualization by fluorescence or radiography, or b) facile separation of the target from an unknown mixture of
15 targets, whether proteinaceous or not proteinaceous. An Example of an affinity reagent according to b) would be biotin either directly attached to (I) or linked with a spacer of one to 50 atoms selected from the group consisting of: C, H, O, N, S, or P in any combination. An Example of an affinity reagent according to a) above would be fluorescein, either directly attached to (I) or linked with a spacer of one to
20 50 atoms selected from the group consisting of: C, H, O, N, S, or P in any combination.

The term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or
25 human that is being sought by a researcher or clinician. The term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease or disorder, or a decrease in the rate of advancement of a disease or disorder, and also includes amounts effective to
30 enhance normal physiological function.

Whenever the terms "aliphatic" or "aryl" or either of their prefixes appear in a name of a substituent (e.g. arylalkoxyaryloxy) they include those characteristics given above for "aliphatic" and "aryl". Aliphatic or cycloalkyl substituents are term
5 equivalents to those having one or more degrees of unsaturation. Designated numbers of carbon atoms (e.g. C₁₋₁₀) refer independently to the number of carbon atoms in an aliphatic or cyclic aliphatic moiety or to the aliphatic portion of a larger substituent in which the term "aliphatic" appears as a prefix (e.g. "al-").

10 As used herein, the term "disubstituted amine" or "disubstituted amino-" includes either one or two substitutions on that particular nitrogen atom.

As used herein, the term "oxo" refers to the substituent =O.

15 As used herein, the term "halogen" or "halo" shall include iodine, bromine, chlorine and fluorine.

As used herein, the term "mercapto" refers to the substituent -SH.

20 As used herein, the term "carboxy" refers to the substituent -COOH.

As used herein, the term "cyano" refers to the substituent -CN.

As used herein, the term "aminosulfonyl" refer to the substituent
25 -SO₂NH₂.

As used herein, the term "carbamoyl" refers to the substituent -C(O)NH₂.

As used herein, the term "sulfanyl" refers to the substituent -S-.

As used herein, the term "sulfenyl" refers to the substituent -S(O)-.

As used herein, the term "sulfonyl" refers to the substituent -S(O)₂-.

5

PHARMACEUTICAL FORMULATION AND DOSES

While it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula I, as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides pharmaceutical compositions which include therapeutically effective amounts of compounds of the formula I and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the formula I and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of the formula I, or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

25 The compounds of the present invention can be administered in such oral (including buccal and sublingual) dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular inhalation or

30

insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

The dosage regimen utilizing the compounds of the present invention is
5 selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug
10 required to prevent, counter or arrest the progress of the condition.

Oral dosages of the present invention, when used for the indicated effects, will range between about 0.1 to about 100 mg/kg of body weight per day, and particularly about 1 to 10 mg/kg of body weight per day. Oral dosage units will
15 generally be administered in the range of from 1 to about 250 mg and more preferably from about 25 to about 250 mg. The daily dosage for a 70 kg mammal will generally be in the range of about 70 mg to 7 grams of a compound of formula I or II.

20 The dosage to be administered is based on the usual conditions such as the physical condition of the patient, age, body weight, past medical history, route of administrations, severity of the conditions and the like. Oral administration is generally preferred for administration to a human. In some cases, a relatively lower dose is sufficient and, in some cases, a relatively higher dose or increased number of
25 doses may be necessary. Topical application similarly may be once or more than once per day depending upon the usual medical considerations. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. The compounds of the invention can be prepared in a range of
30 concentrations for topical use of about 0.5 to about 5mg/ml of suitable solvent. A

preferred volume for application to the scalp is about 2 ml, resulting in an effective dosage delivered to the patient of about 1 to about 10mg.

In the methods of the present invention, the compounds herein described in
5 detail can form the active ingredient and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

10

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a
15 similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture as described above, and
20 filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

25

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or
30 sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a
5 powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an algininate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a
10 quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs
15 broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging
20 steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit
25 form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy

ethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for Example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

25

The present invention includes pharmaceutical compositions containing about 0.01 to about 99.5%, more particularly, about 0.5 to about 90% of a compound of the formula (II) in combination with a pharmaceutically acceptable carrier.

30

Parenteral administration can be effected by utilizing liquid dosage unit forms such as sterile solutions and suspensions intended for subcutaneous, intramuscular or intravenous injection. These are prepared by suspending or dissolving a measured amount of the compound in a non-toxic liquid vehicle
5 suitable for injection such as aqueous oleaginous medium and sterilizing the suspension or solution.

Alternatively, a measured amount of the compound is placed in a vial and the vial and its contents are sterilized and sealed. An accompanying vial or vehicle
10 can be provided for mixing prior to administration. Non-toxic salts and salt solutions can be added to render the injection isotonic. Stabilizers, preservations and emulsifiers can also be added.

Rectal administration can be effected utilizing suppositories in which the
15 compound is admixed with low-melting water-soluble or insoluble solids such as polyethylene glycol, cocoa butter, higher ester as for Example flavored aqueous solution, while elixirs are prepared through myristyl palmitate or mixtures thereof.

Topical formulations of the present invention may be presented as, for
20 instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.
25 Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from
30 pressurized packs or a nebulizer, with the use of a suitable propellant, e.g.

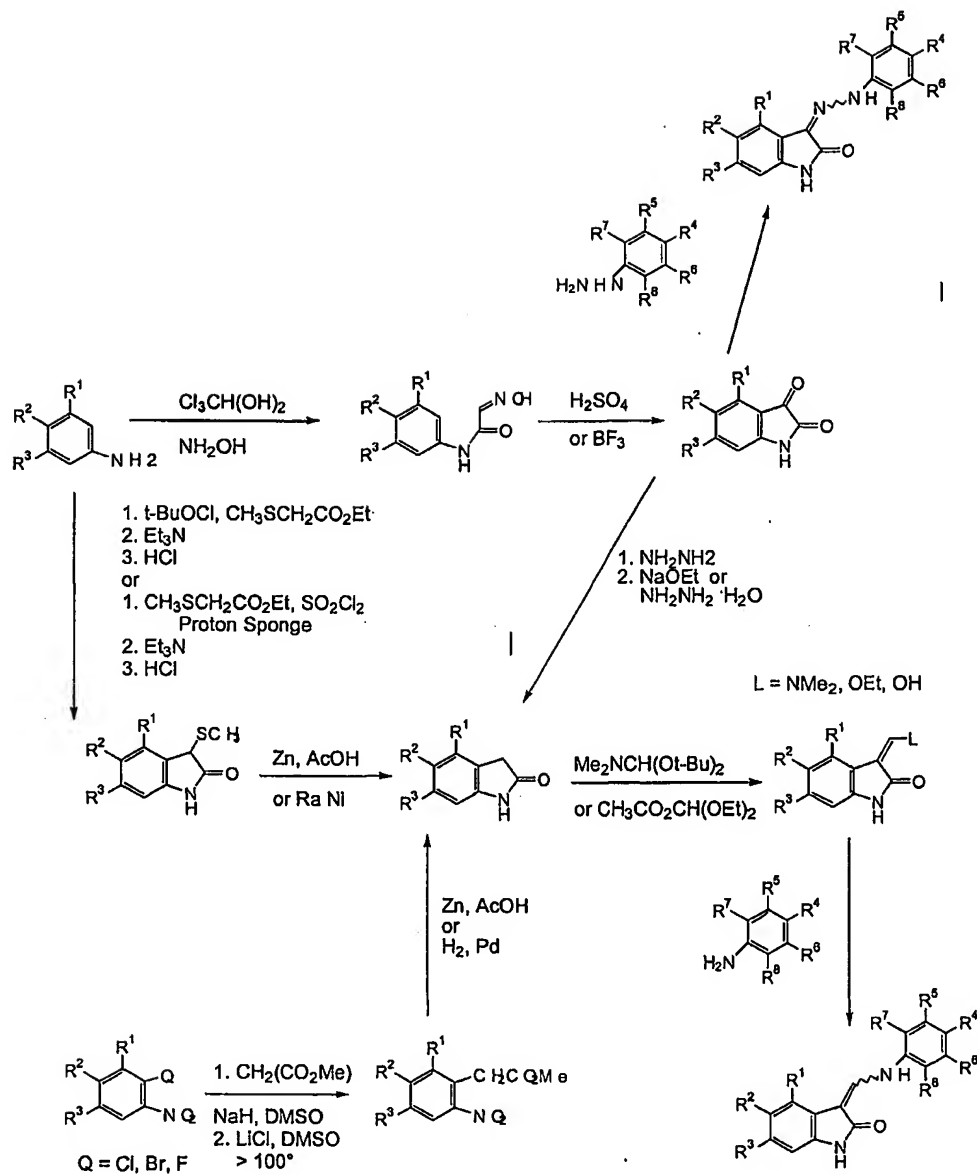
dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an
5 inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

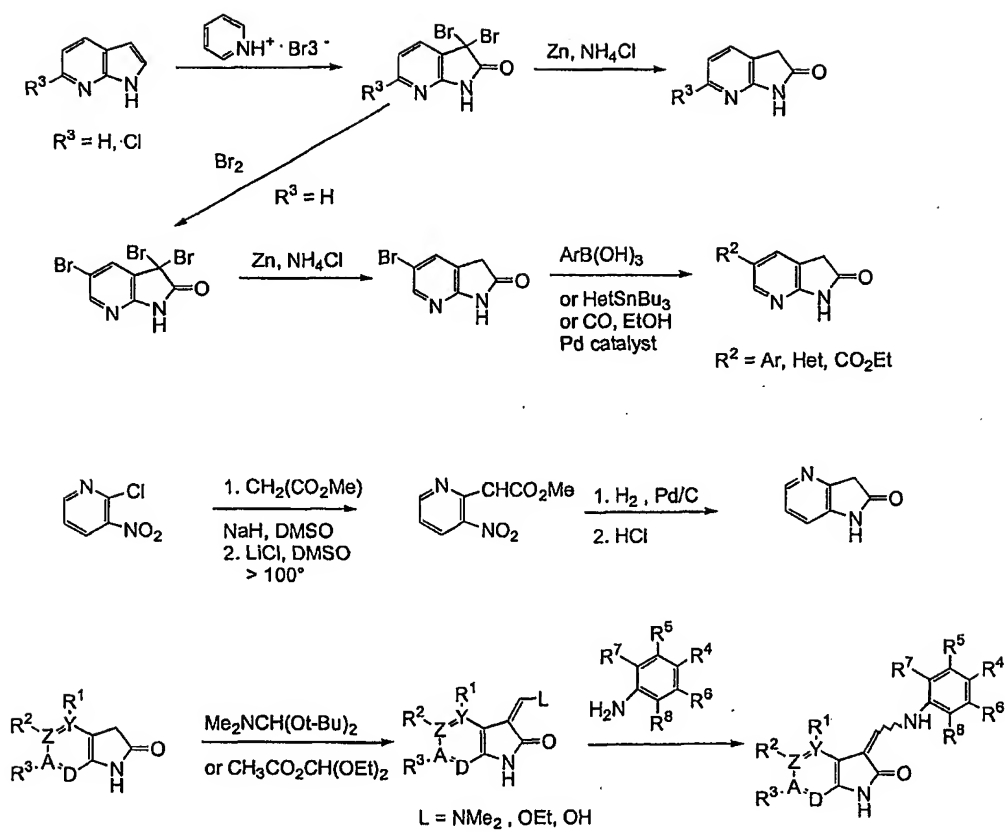
The preferred pharmaceutical compositions are those in a form suitable for oral administration, such as tablets and liquids and the like and topical formulations.

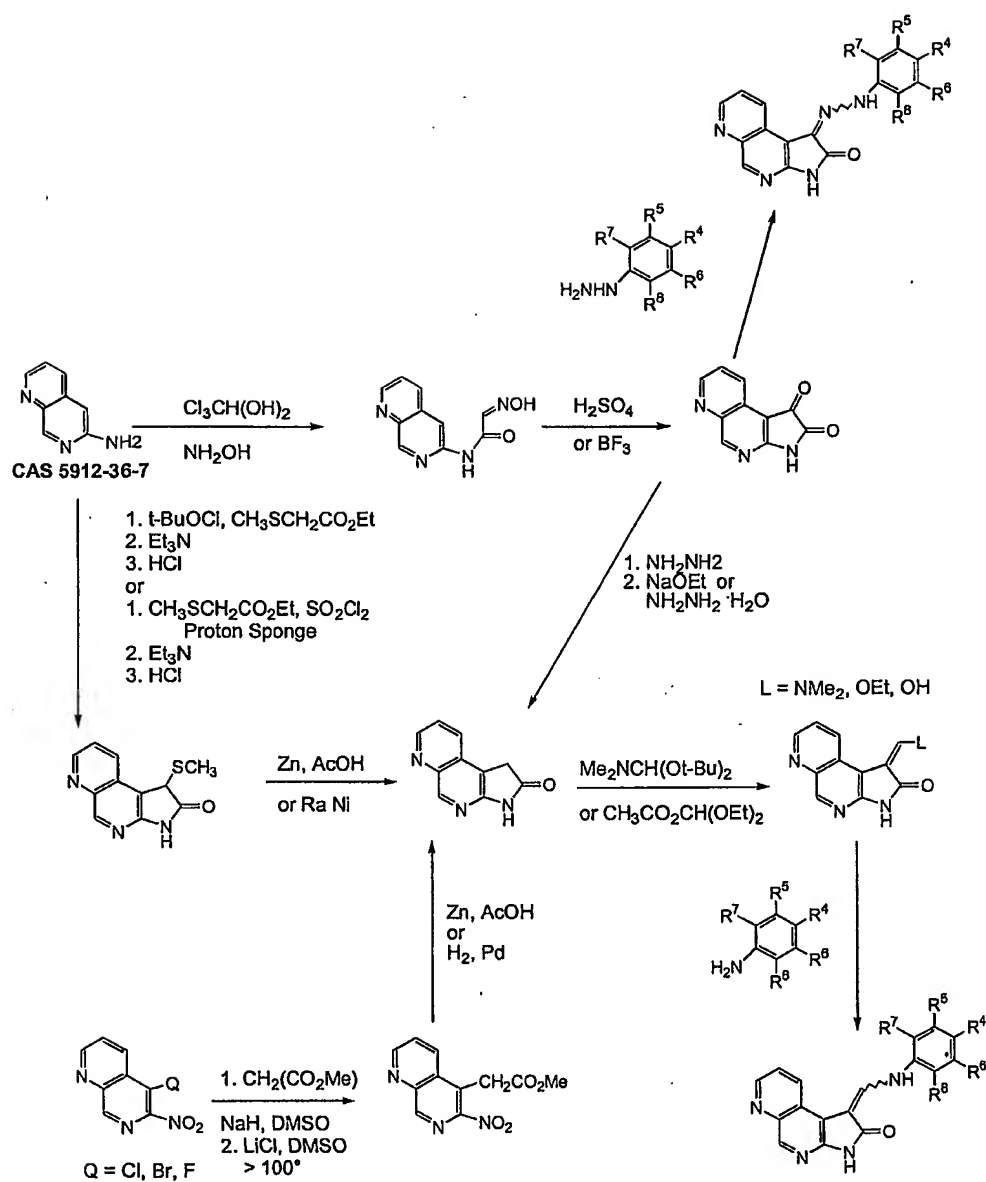
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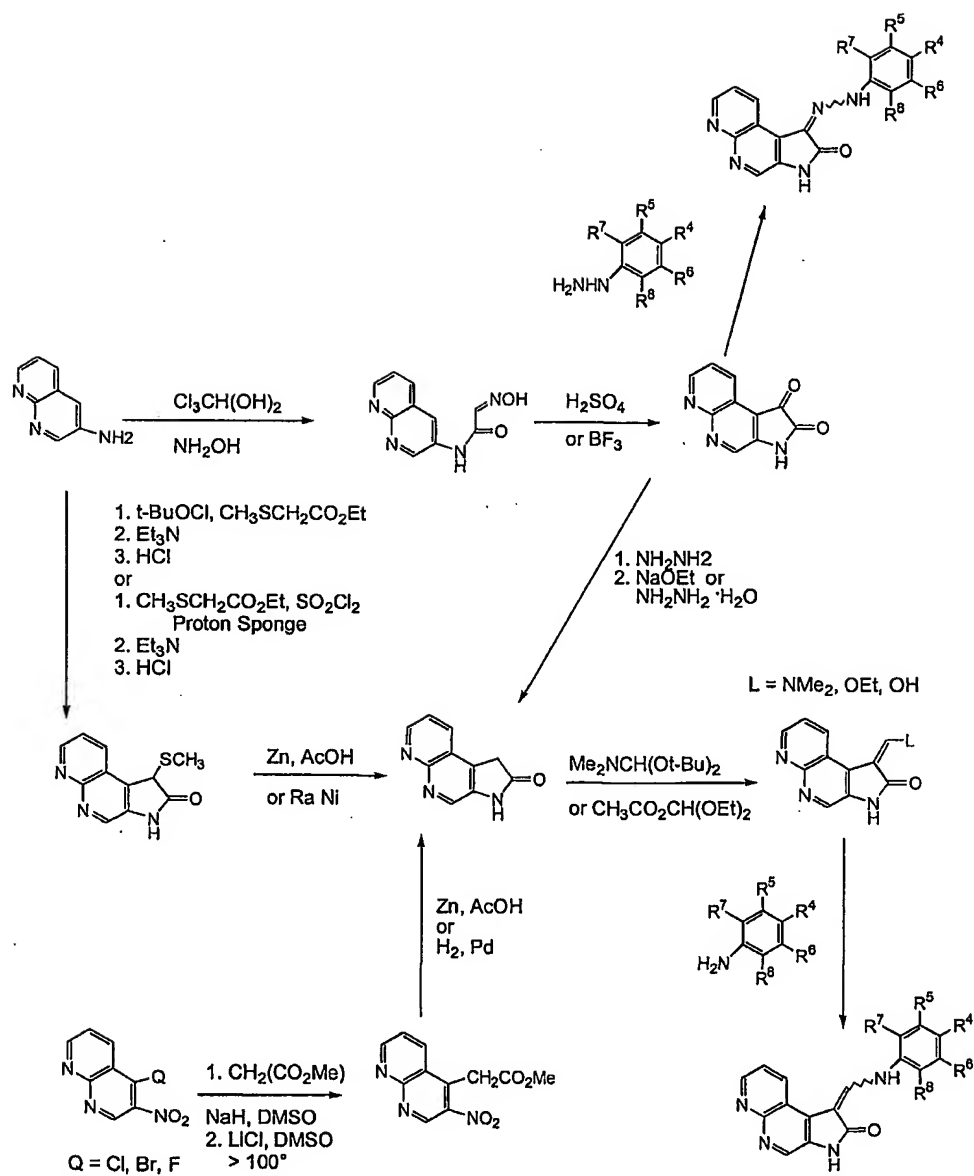
The compounds of formula (I) can be prepared readily according to the following reaction General Synthesis Schemes (in which all variables are as defined before) and Examples or modifications thereof using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is
15 also possible to make use of variants, which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

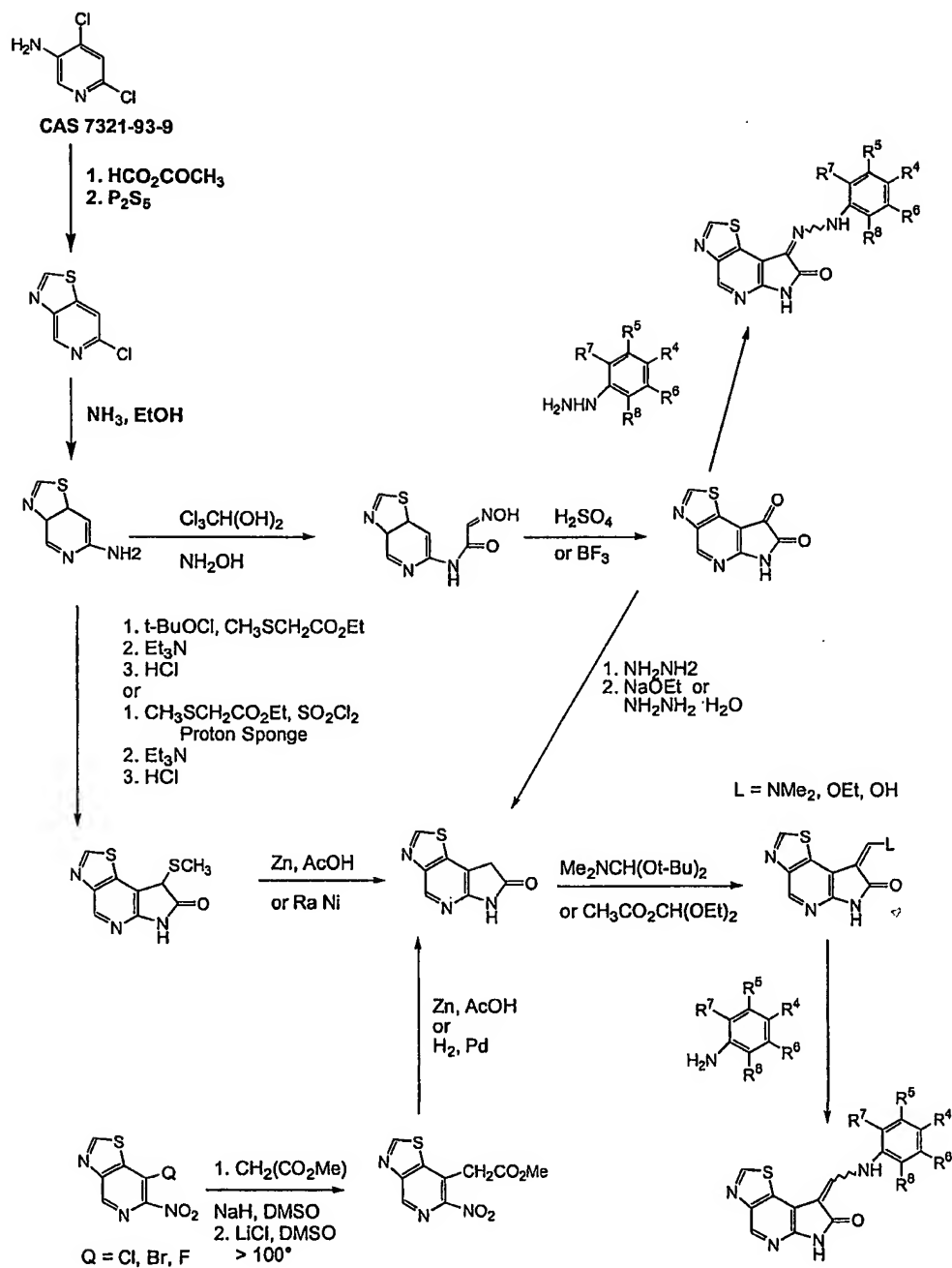
General Synthesis Schemes











The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless noted otherwise.

10

Abbreviations used in the Examples are as follows:

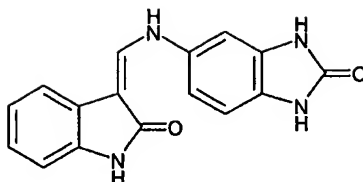
g	= grams
mg	= milligrams
L	= liters
15 mL	= milliliters
M	= molar
N	= normal
mM	= millimolar
i.v.	= intravenous
20 p.o.	= per oral
s.c.	= subcutaneous
Hz	= hertz
mol	= moles
mmol	= millimoles
25 mbar	= millibar
psi	= pounds per square inch
rt	= room temperature
min	= minutes
h	= hours
30 mp	= melting point

	TLC	= thin layer chromatography
	R _f	= relative TLC mobility
	MS	= mass spectrometry
	NMR	= nuclear magnetic resonance spectroscopy
5	APCI	= atmospheric pressure chemical ionization
	ESI	= electrospray ionization
	m/z	= mass to charge ratio
	t _r	= retention time
	Pd/C	= palladium on activated carbon
10	ether	= diethyl ether
	MeOH	= methanol
	EtOAc	= ethyl acetate
	TEA	= triethylamine
	DIEA	= diisopropylethylamine
15	THF	= tetrahydrofuran
	DMF	= N, N-dimethylformamide
	DMSO	= dimethylsulfoxide
	DDQ	= 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
	LAH	= lithium aluminum hydride
20	TFA	= trifluoroacetic acid
	LDA	= lithium diisopropylamide
	THP	= tetrahydropyranyl
	NMM	= N-methylmorpholine, 4-methylmorpholine
	HMPA	= hexamethylphosphoric triamide
25	DMPU	= 1,3-dimethoxypropylene urea
	d	= days
	ppm	= parts per million
	kD	= kiloDalton
	LPS	= lipopolysaccharide
30	PMA	= phorbol myristate acetate

SPA	= scintillation proximity assay
EDTA	= ethylenediamine tetraacetic acid
FBS	= fetal bovine serum
PBS	= phosphate buffered saline solution
5 BrdU	= bromodeoxyuridine
BSA	= bovine serum albumin
FCS	= fetal calf serum
DMEM	= Dulbeccos modified Eagle's medium
pfu	= plaque forming units
10 MOI	= multiplicity of infection

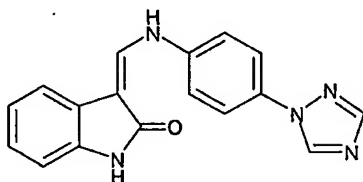
Reagents are commercially available or are prepared according to procedures in the literature. The physical data given for the compounds exemplified is consistent with the assigned structure of those compounds. ¹H NMR spectra were obtained on
15 VARIAN Unity Plus NMR spectrophotometers at 300 or 400 Mhz. Mass spectra were obtained on Micromass Platform II mass spectrometers from Micromass Ltd. Altrincham, UK, using either Atmospheric Chemical Ionization (APCI) or Electrospray Ionization (ESI). Analytical thin layer chromatography (TLC) was used to verify the purity of some intermediates which could not be isolated or which were too unstable
20 for full characterisation, and to follow the progress of reactions. Unless otherwise stated, this was done using silica gel (Merck Silica Gel 60 F254). Unless otherwise stated, column chromatography for the purification of some compounds, used Merck Silica gel 60 (230-400 mesh), and the stated solvent system under pressure.

25 *Example 1: Preparation of 5-{[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}-1,3-dihydro-2H-benzimidazol-2-one*



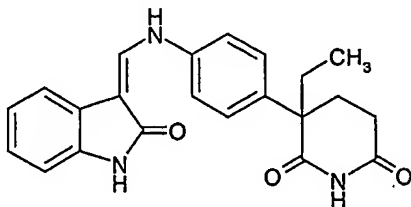
A solution of 161 mg (1.00 mMol) of 3-(hydroxymethylene)-1,3-dihydro-2H-indol-2-one, 149 mg (1.00 mMol) of 5-aminobenzimidazolone, and 5 ml of ethanol was heated at 55 °C for 1.5 hr. The resulting solid was isolated by filtration and 5 recrystallized from DMSO/methanol to yield 150 mg (51%) of a yellow solid, ¹H NMR (DMSO-d₆): δ 6.80 (d, J = 7.7 Hz, 1H), 6.85-6.98 (m, 4H), 7.00 (s, 1H), 7.54 (d, J = 7.4 Hz, 1H), 8.50 (d, J = 12.7 Hz, 1H), 10.39 (s, 1H), 10.56 (s, 1H), 10.72 (d, J = 12.7 Hz, 1H), 10.74 (s, 1H); APCI-MS *m/z* 291 (M-H)⁺.

10 **Example 2: Preparation of (3Z)-3-{[4-(1H-1,2,4-triazol-1-yl)anilino]-methylene}-1,3-dihydro-2H-indol-2-one**



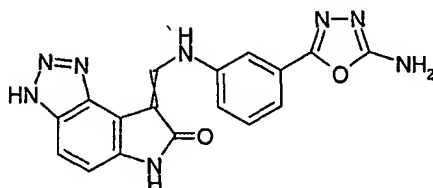
Prepared in an analogous manner to Example 1 using 1 equivalent of 4-(1H-1,2,4-triazol-1-yl)aniline in place of 5-aminobenzimidazolone. ¹H NMR (DMSO-d₆): δ 10.80 15 (m, 1H); 10.52 (s, 1H); 9.26 (s, 1H); 8.62 (m, 1H); 8.22 (s, 1H); 7.86 (m, 2H); 7.60 (m, 3H); 7.02 (m, 1H); 6.94 (m, 1H); 6.85 (m, 1H). APCI MS (+ve) 304. APCI MS (-ve) 302.

Example 3: Preparation of 3-ethyl-3-(4-{[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}phenyl)-2,6-piperidinedione



Prepared in an analogous manner to Example 1 using one equivalent of 3-ethyl-3-(4-(aminophenyl)-2,6-piperidinedione in place of 5-aminobenzimidazolone. ¹H NMR (400 MHz, d₆-DMSO) δ 10.91 (s, 1H), 10.73 (d, 1H, J=12.5Hz), 10.52 (s, 1H), 8.58 (d, 1H, J=12.5Hz), 7.59 (d, 1H, J=7.4Hz), 7.43 (d, 2H, J=8.6Hz), 7.31 (d, 2H, J=8.6Hz), 7.1 - 6.85 (m, 3H), 2.48 - 2.4 (m, 2H), 2.2 - 2.1 (m, 2H), 2.0 - 1.8 (m, 2H), 0.795 (t, 2H, J=7.3Hz), MS (AP+, m/z) 376 (M+H).

Example 4: Preparation of (8Z)-8-{[3-(5-amino-1,3,4-oxadiazol-2-yl)anilino]methylene}-6,8-dihydro[1,2,3]triazolo[4,5-e]indol-7(3H)-one



10

Prepared in an analogous manner to Example 1 using 1 equivalent of 8-dimethylaminomethylene-1-tert-butyloxycarbonyl-1,6-dihydro[1,2,3]triazolo[4,5-e]indol-7-one and 3-(2-(5-amino)-oxadiazoyl)-aniline. APCI MS (-ve) 359.

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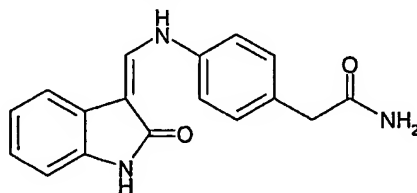
Preparation of 8-dimethylaminomethylene-1-tert-butyloxycarbonyl-1,6-dihydro[1,2,3]triazolo[4,5-e]indol-7-one

5-Aminobenzotriazole (Lancaster Chemical, 10.14 g, 75 mmol) was dissolved in 200 ml of anhydrous DMF under nitrogen and 3.00 g (75 mmol) of sodium hydride (60% oil dispersion) was added in one portion. Hydrogen evolution and mild exothermicity was observed. The reaction was stirred at room temperature for 20 minutes and then cooled in an ice bath. A solution of di-tert-butylidicarbonate (16.4 g, 75 mmol) in 100 ml of anhydrous DMF was added via siphon. Stirring was continued for 2 hrs at ice bath temperature. The solvent was removed by rotary evaporation under high vacuum at 50 °C to give 32 g of viscous liquid. The crude product was dissolved in a minimum volume of chloroform and filtered through a short column of 600 ml silica gel, eluting with 10% methanol in chloroform. The collected product was

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evaporated to dryness, redissolved in 400 ml of diethyl ether, and washed three times with water and once with saturated sodium chloride solution. The ether solution was dried over magnesium sulfate and the solvent was removed to give 17.7 g of a mixture of 1- and 3-tert-butyloxycarbonyl-5-aminobenzotriazole
5 contaminated with approx. 1 g of residual mineral oil. This material was then cyclized to the corresponding 3-methylthio-oxindole by the method of Procedure (Gassman). The resultant product (9.6 g of gray solid) was shown to be partially deprotected by NMR. This material was dissolved 200 ml of THF and treated with 50 g of zinc dust (activated by stirring for 10 min in 150 ml of 1 M HCl, followed by
10 washing with three 100 ml portions of water). Saturated aqueous ammonium chloride (150 ml) was added and the reaction was stirred overnight at room temperature. The solution was filtered through Celite, washing with THF and ethyl acetate to give 4.0 g of gray solid which was primarily 1-tert-butyloxycarbonyl-1,6-dihydro[1,2,3]triazolo[4,5-e]indol-7-one. This material (2.04 g, 7.4 mmol) was
15 suspended in 10 ml of anhydrous DMF under nitrogen, cooled in an ice bath, and treated with 4.0 ml (3.4 g, 2.2 equiv) of dimethylformamide di-tert-butyl acetal. The reaction was allowed to warm to room temperature and was stirred overnight. The solvent was removed by rotary evaporation under high vacuum. The residue was filtered through a short column of 100 ml silica gel with 30% ethanol in
20 dichloromethane. Evaporation of solvent provided 1.74 g of yellow solid which was primarily 8-dimethylaminomethylene-1-tert-butyloxycarbonyl-1,6-dihydro[1,2,3]triazolo[4,5-e]indol-7-one containing some product lacking the tert-butyloxycarbonyl protecting group.

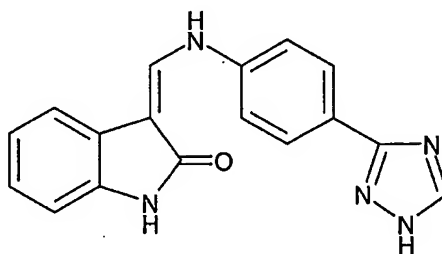
25 *Example 5: Preparation of 2-(4-{[(Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]amino}phenyl)acetamide*



A mixture of 0.214 g (1.33 mmol) of (3*Z*)-3-(hydroxymethylene)-1,3-dihydro-2*H*-indol-2-one^{1,2} and 0.200 g (1.33 mmol) of 4-aminophenylacetamide³ in 5 ml of EtOH was heated to 80 °C for 1 hr. After cooling to ambient temperature, the solid was collected by vacuum filtration and dried in a vacuum oven at 60 °C to afford 2-(4-
 5 {[(*Z*)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]amino}phenyl)acetamide (0.15 g, 37%). mp > 250 °C; ¹H NMR (DMSO-*d*₆): δ 3.36 (s, 2H), 6.81-7.08 (m, 4H), 7.27 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 7.47 (s, 1H), 7.60 (d, J = 7.3 Hz, 1H), 8.59 (d, J = 12.5 Hz, 1H), 10.51 (s, 1H), 10.73 (d, J = 12.5 Hz, 1H); APCI-MS: *m/z* 292 (m-H)⁺. Anal. Calcd for C₁₇H₁₅N₃O₃: C, 69.61; H, 5.15; N, 14.33%. Found: C, 69.54; H, 5.20; N,
 10 14.37%.

(1) Wolfbeis, Otto S.; Junek, Hans. Diacylenamines and -enols, III. Formylation of CH₂-acidic compounds via the anilinomethylene derivatives. Z. Naturforsch., B: Anorg. Chem., Org. Chem. (1979), 34B(2), 283-9. (2) Winn, Martin; Kyncl, John J. Aminomethylene oxindoles. U.S. (1979), 6 pp (3) Clark, C. Randall; Davenport,
 15 Timothy W. Anticonvulsant activity of some 4-aminophenylacetamides. J. Pharm. Sci. (1987), 76(1), 18-20.

*Example 6: Preparation of (3*Z*)-3-{[4-(1*H*-1,2,4-triazol-3-yl)anilino]methylene}-1,3-dihydro-2*H*-indol-2-one*



20

Prepared in an analogous manner to Example 1 using one equivalent of 4-(1*H*-1,2,4-triazol-3-yl)aniline in place of 5-aminobenzimidazolone. ¹H NMR (400 MHz, *d*₆-DMSO) δ 14.32 (s, 1H, exchangeable); 14.05 (s, 1H, exchangeable); 10.82 (m, 1H); 10.54 (m, 1H); 8.64 (m, 1H); 8.60 (s, 1H, exchangeable); 8.00 (m, 2H); 7.63 (m, 1H);
 25 7.47 (m, 1H); 7.03 (m, 1H); 6.94 (m, 1H); 6.85 (m, 1H). APCI MS (-ve) 302.

BIOLOGICAL DATA

The compounds of the present invention have valuable pharmacologic properties. Different compounds from this class are particularly effective at inhibiting the trkA kinase enzyme at concentrations that range from 0.0001 to 1 μ M and additionally show specificity relative to other kinases. Substrate phosphorylation assays were carried out as follows:

Screening format: Tyrosine kinase activity is being measured using a synthetic peptide substrate. The enzyme is a GST-fusion of the intracellular domain expressed in SF9 cells. The enzyme is expressed and purified by Regeneron. The enzyme is preincubated with cold ATP and Mg to allow autophosphorylation prior to running the screen. This increases the initial rate of catalysis approximately 3 fold. The assay is performed in 96 well microtitre plates, and reaction products are detected following filtration through millipore p81 phosphocellulose plates.

Assay conditions

Peptide substrate	Src peptide, NH ₂ - RRRAAAEEIYGEI- NH ₂
Peptide Km	60 μ M
ATP Km	30 μ M
Kcat/Km (peptide):	1 x 10 ⁴
Assay conditions	20 – 40 nM TrkA, 30 μ M ATP, 50 μ M Src peptide, 50 mM MOPS pH 7.5, 10 mM MgCl ₂ , 0.6 μ Ci ³³ P-ATP
Incubation	RT for 120'
Termination	Add 100 μ l of 0.5% Phosphoric acid. Spot 100 μ l onto millipore p81 96 well filter plate. Filter, wash 3x with 200 μ l 0.5 % phosphoric acid. Add 50 μ l scintillation cocktail. Count in Packard Topcount

Representative results are shown in Table 1 for the TrkA tyrosine kinase inhibition

Table 1

	Substrate Phosphorylation
Example	TrkA
1	+++
2	+++
3	+++
4	+++
5	++
6	++

5

IC ₅₀ values	Symbol
< 0.010 uM	+++
0.010 – 0.10 uM	++
0.10 – 1.0 uM	+
> 1.0 uM	-
Not determined	ND

10

UTILITY OF INVENTION

Inhibitors of Trk tyrosine kinase have utility as agents in the treatment of a wide variety of disorders. These include, for example, cancers and chronic pain.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages
5 other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for cancer conditions, or for other indications for the compounds of the invention as indicated above. Likewise, the specific pharmacologic responses observed may vary according to and depending upon the particular active compound selected or
10 whether there are present certain pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims, which follow, and that such claims be
15 interpreted as broadly as is reasonable.

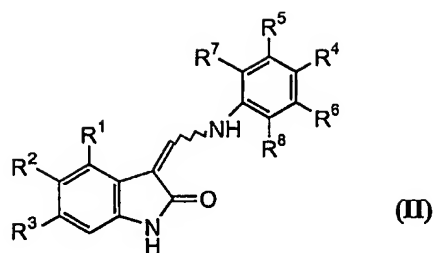
The application of which this description and claim(s) forms part may be used as a basis for priority in respect of any subsequent application. The claims of such
20 subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, formulation, process or use claims and may include, by way of example and without limitation, one or more of the following claim(s):

Claims

We claim:

1. A compound of the formula II:

5



or salts, solvates, or physiological functional derivatives thereof

10

wherein:

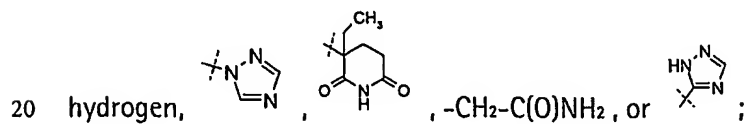
R¹ is hydrogen;

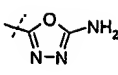
R² is hydrogen; or

15 R¹ and R² are optionally joined to form a fused ring Het, wherein Het is a triazine ring;

R³ is hydrogen;

R⁴ is selected from the group consisting of



R⁵ is hydrogen or , or

R⁴ and R⁵ are optionally joined to form a fused cyclic urea ring; and

5 R⁶, R⁷, and R⁸ are hydrogen.

2. A compound selected from the group:

- 10 5-{[(Z)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]amino}-1,3-dihydro-2*H*-benzimidazol-2-one;
 (3*Z*)-3-{[4-(1*H*-1,2,4-triazol-1-yl)anilino]-methylene}-1,3-dihydro-2*H*-indol-2-one;
 3-ethyl-3-(4-{[(Z)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]amino}phenyl)-2,6-piperidinedione;
 15 (8*Z*)-8-{[3-(5-amino-1,3,4-oxadiazol-2-yl)anilino]methylene}-6,8-dihydro[1,2,3]triazolo[4,5-*e*]indol-7(3*H*)-one;
 2-(4-{[(Z)-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene) methyl]amino}phenyl)acetamide; and
 (3*Z*)-3-{[4-(1*H*-1,2,4-triazol-3-yl)anilino]methylene}-1,3-dihydro-2*H*-indol-2-one;
 20 or salts, solvates or physiologically functional derivatives thereof.

3. A pharmaceutical composition, comprising: a therapeutically effective amount of a compound as claimed in claim 1 or 2, or a salt, solvate, or a physiologically functional derivative thereof and one or more of pharmaceutically
 25 acceptable carriers, diluents and excipients.

4.. A method of treating a disorder in a mammal, said disorder being mediated by inappropriate TrkA activity, comprising: administering to said mammal a

therapeutically effective amount of a compound as claimed in claim 1 or 2, or salt, solvate, or a physiologically functional derivative thereof.

5. The method of claim 4, wherein the disorder is pain.

5

6. The method of claim 4, wherein the disorder is cancer.

7. A compound as claimed in claim 1 or 2, or a salt, solvate, or a physiologically functional derivative thereof for use in therapy.

10

8. Use of a compound as claimed in claim 1 or 2, or a salt, solvate, or a physiologically functional derivative thereof in the preparation of a medicament for use in the treatment of a disorder mediated by inappropriate TrkA activity.

15 9. The use of claim 8, wherein the disorder is pain.

10. The use of claim 8, wherein the disorder is cancer.

11. A method of treating pain in a mammal, comprising: administering to said
20 mammal a therapeutically effective amount of a compound as claimed in claim 1 or 2, or a salt, solvate, or a physiologically functional derivative thereof.

12. A method of treating cancer in a mammal, comprising: administering to said
mammal a therapeutically effective amount of a compound as claimed in claims 1
25 or 2, or a salt, solvate, or a physiologically functional derivative thereof.

13. A method of treating a disorder in a mammal, said disorder being mediated
by inappropriate mitogen activated kinase activity, comprising: administering to
said mammal a therapeutically effective amount of a compound as claimed in claim
30 1 or 2 or a salt, solvate, or physiologically functional derivative thereof.

14. The method of claim 13, wherein the disorder is pain.
- 5 15. The method of claim 13, wherein the disorder is cancer.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 01/26286

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/12 C07D401/12 C07D487/04 C07D209/14 A61P29/00
A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 99 15500 A (GLAXO GROUP LTD ; FRYE STEPHEN VERNON (US); HARRIS PHILIP ANTHONY () 1 April 1999 (1999-04-01) claim 1</p> <p>--- -/-</p>	1-15

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

18 January 2002

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/26286

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	DE 198 24 922 A (BOEHRINGER INGELHEIM PHARMA) 9 December 1999 (1999-12-09) claim 1 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/26286

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